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CONTROL OF TUBERCULOSIS IN A NEUROPSYCHIATRIC HOSPITAL*

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IN the past few years, organized efforts for the control of tuberculosis have been recognized as essential in mental institutions. For effective control of the spread of tuberculosis in any community a program must ensure early case finding, facilitate prompt isolation, diagnosis and treatment and educate the community to co-operate in enforcing the program. The measures employed at the Veterans Administration Hospital at Bedford, Massachusetts, are the same as those in any community, except that more rigid steps are required because of the greater incidence of tuberculosis in mental hospitals.

Mental patients have a tendency to conceal constitutional symptoms, but if they do reveal them the symptoms may be unreliable. Loss of appetite, fatigability, cough, expectoration and night sweats are rarely mentioned, and objective symptoms such as loss of weight, which may be the result of refusal to eat, and hemoptysis may be misinterpreted; blood mixed with saliva from self-inflicted abrasions in the nasal or buccal cavities may resemble hemoptysis. Persistent afternoon elevations of temperature, productive cough and true hemoptysis are valuable aids to diagnosis. Therefore, serial x-ray examinations, repeated concentrated and cultured examinations of sputum or gastric washings, erythrocyte sedimentation rate, Mantoux tests and objective findings are the principal means of detecting tuberculosis early in mental patients.

This paper concerns problems of control, diagnosis and treatment of tuberculosis peculiar to a neuropsychiatric hospital.

CASE FINDING

Early case finding is accomplished principally by means of x-ray examinations of every patient and employee in the hospital at least once a year; all patients with inactive tuberculosis have periodic chest x-ray films at least every three months and more frequently when indicated. Every film is studied by the visiting roentgenologist, and persons showing disease are referred to the physician in charge of the Tuberculosis Unit. When films give evidence or are suggestive of active tuberculosis appropriate steps are taken: in 1952, 19 patients were admitted to the Tuberculosis Unit from other wards in the hospital, 3 employees were sent to the United States Public Health Service Hospital, and 1 affiliate student nurse was hospitalized at Essex County Sanatorium. Mantoux tests have been given to the entire hospital personnel, consisting of 1050 permanent employees and 35 affiliate student nurses, and all patients, personnel and affiliate student nurses are given skin tests and x-ray examinations on beginning and x-ray study on terminating their connection with the hospital. Negative skin reactors are retested every three months, and positive reactors with previously negative tests are given x-ray examinations every three months for eighteen months.

ISOLATION

Patients with Active Disease

If at any time it becomes evident that a patient has active tuberculosis he is assigned a bed in the appropriate dormitory in the Tuberculosis Unit and treatment is started without delay; x-ray films of all patients in the ward where he previously resided are promptly taken. In doubtful cases the patient is kept in isolation as long as is necessary to decide whether or not active tuberculosis exists.

Patients with Tuberculosis on Admission to Hospital

Patients admitted to the hospital with known active tuberculosis are sent directly to the Tuberculosis Unit on arrival, as are those with active tuberculosis detected by x-ray study on admission. In 1952, 19 such patients were admitted directly to the Unit on admission.

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Retention of Inactive Cases in Tuberculosis Unit

Because of the high incidence of tuberculosis in mental institutions and because of the need for prolonged convalescent supervision, patients who have reached the inactive stage are retained in the Tuberculosis Unit for an indefinite period. When such patients are transferred to other buildings in the hospital they do not receive the sheltered care that their disease requires, and reactivations are more frequent.

Sanitary Precautions in Tuberculosis Unit

Caps, gowns and masks are worn by employees and visitors at all times in the active sections of the Unit. The protective material is kept in a wardrobe in the lobby (clean area) and is put on as soon as the person enters the Unit from the elevator. It is worn until he prepares to leave the Unit or enter a clean area. Then he steps into the decontamination room and discards the protective material into receptacles provided for the purpose, which, with their contents, are sterilized several times a day. He then washes and dries his hands and leaves the decontamination room.

Meticulous cleanliness, frequent scrubbing of hands, oiling of floors, careful sterilization of all contaminated material, proper handling of laundry and food conveyers, and incineration of garbage and contaminated dispensable material are employed at all times.

Diagnosis

One of the problems encountered in mental institutions is the difficulty of obtaining adequate sputum specimens. Most mental patients do not expectorate their sputum, nor can they be depended on to collect satisfactory specimens. The sputum cup, if it is not lost or destroyed, is usually contaminated by other patients' sputum or various miscellaneous material. A method devised here of collecting sputum specimens has eliminated the need of many examinations of gastric washings. A sputum cup for each patient from whom a specimen is desired is marked with his name in red crayon on the top lid. These cups are placed on a metal tray, and taken around by an attendant the first thing in the morning and at intervals during the day. Each patient is encouraged to expectorate into his individual cup, and between times the tray of cups is kept in a safe place.

Obtaining gastric specimens is also much more difficult than under ordinary conditions because of the patient's resistance to the procedure. Furthermore, to ensure a fasting specimen, it is necessary to keep the patient under constant observation by an attendant from the time he wakes up in the morning of the day on which the procedure is performed until the specimen is obtained. Sputum and gastric specimens are sent promptly to the laboratory, where they are concentrated, stained, examined and cultured by the usual methods. The laboratory employs a full-time bacteriologist in addition to the usual technicians and personnel, and is equipped with facilities for animal inoculation and sensitivity testing.

The difficulty in obtaining satisfactory x-ray films of disturbed patients has been largely overcome by expert handling by the x-ray technicians, so that a sedative is seldom required.

Bronchoscopic and bronchographic studies are performed by either the consultant chest surgeon or the otolaryngologist but more often by the former. In no case has the procedure been withheld or abandoned because of disturbed behavior.

Treatment

The treatment of tuberculosis at this hospital is identical with the conventional methods practiced in tuberculosis hospitals all over the country, except that the abnormal behavior of patients frequently requires variations in details. For example, many patients with paranoid ideas may think they are being punished when they are ordered to remain in bed, or being poisoned when given medicine, whereas others are agitated and some assaultive and occasionally one refuses to eat. These peculiarities interfere with the progress of treatment, but certain conditions in a neuropsychiatric hospital serve as aids to treatment. For example, legal commitment to the institution, eliminating absence without leave and inebriety, prevents interruption of treatment; also, prompt admission to the Tuberculosis Unit frequently checks the disease in its incipient stage.

Although some mental patients are hard to handle and refuse treatment many accept treatment without protest. On the whole, they complain less, appear less dissatisfied and accustom themselves to stay in bed with less resentment than patients in other hospitals.

In the Tuberculosis Unit segregation is governed not only by the status of the pulmonary disease but also by the character of the mental disease. It is essential to separate the quiet from the noisy, the clean from the untidy and the co-operative from the unruly, and to provide seclusion for certain disturbed patients during their periods of manic behavior. A patient who is quiet and co-operative may suddenly become noisy or even violent, requiring transfer to a dormitory for disturbed patients or seclusion. In addition all these patients must be separated according to the status of their pulmonary disease — that is, whether it is active, arrested or inactive.

A large dormitory of 17 beds is occupied by tidy, quiet patients with active tuberculosis who require bed rest. In this dormitory quiet is maintained at all times, and as soon as any patient becomes excited or noisy he is transferred to the dormitory for disturbed patients which accommodates 16 patients with active tuberculosis who require constant supervision by an attendant. Another large dormitory accommodates 19 ambulatory patients with inactive disease, all of whom

are kept entirely separate from other patients in the Tuberculosis Unit and eat in a separate dining room; they enjoy all the privileges to which patients in other buildings in the hospital are entitled, such as passes, ball games, picnics, entertainment, library and rehabilitation shops. The small dormitories and single rooms are occupied by patients with arrested disease, untidy ones with inactive and active cases, patients under observation for activity and all who are seriously ill. Separate toilets and shower accommodations are provided for the different groups.

Patients with inactive and arrested disease perform graduated exercise, consisting of walking outdoors when the weather permits, and the plan of the sheltered rehabilitation workshops is used in suitable cases.

Occupational therapy, which has a significant part in treatment, is under the direction of a full-time occupational therapist, who has obtained gratifying results by awakening interest in projects suitable to individual physical and mental capabilities.

The purposes of the program include improving the patient's daily social life and his relation with other patients and personnel; arousing his interest and thereby helping him develop a rational attitude to his treatment; suggesting improvements and changes in ward housekeeping that will reduce tension by giving an appearance of comfort and an atmosphere of relaxation; and creating a congenial atmosphere by occupational therapy conducted as a cultural and social program.

The coexistence of physical and mental disease greatly limits the choice of projects. For example, all strenuous exertion is contraindicated, as well as materials that can be spilled, thrown or swallowed.

As a rule an initial project is selected that will require little mental effort and minimal physical exertion. So far as possible the selection of the project is left to the patient because a permissive attitude affords some measure of support to his pride, self-respect and individuality. However, variety, safety, health precautions, proper posture and psychologic timing must be given due consideration.

Diversified activities calculated to supplement craft activities when interest lags are supplied by music appreciation, oral expression, discussion of current events, games, puzzles, literature, library service, radio and television.

When a patient with active disease is admitted to the Tuberculosis Unit his mental and general physical condition is studied along with his lung disease, and, before specific therapy is started, a long range estimate of treatment is carefully considered. Consultants in all departments of psychiatry, medicine and surgery are available.

Bed rest is considered of paramount importance in specific therapy, although when patients cannot be persuaded to stay in bed restraint or force is not employed. The intelligent efforts of a staff of nurses and psychiatric aides, specially trained and directed by a charge nurse thoroughly familiar with the problems of the Tuberculosis Unit, make many difficult patients more amenable to bed rest and treatment. At times it requires considerable tact, kindness and understanding to convince the patient that the purpose of the medication and bed rest is to help him get well and not to poison or punish him. In many cases, by engaging him in friendly conversation, sympathetically listening to his delusions, respecting his whims and fantasies or employing firm persuasion tactfully, one will gain the patient's confidence and co-operation so that he will accept nourishment, medication and bed rest.

Bed rest is graduated according to the requirements of the patient. One with new, active disease or with old, extensive, active disease may be assigned to complete bed rest or to complete bed rest with toilet privileges. As his symptoms abate dining-room privileges may be added, and later he may be allowed out of bed one hour a day, then two hours and still later four hours. Before the disease is classified as inactive the patient must have been ambulatory for six months, and the case must meet the requirements for inactive disease specified by the National Tuberculosis Association, 1950.[1] All patients in the Tuberculosis Unit observe a two-hour period of bed rest after the noon meal every day.

Sedatives are used sparingly but are occasionally required to provide needed rest. In extreme episodes of manic behavior three hours spent in a wet pack may assure respite from a long period of excitement by affording several hours of natural sleep, and, in many cases, may terminate the episode. Electric-shock treatment has been used with excellent results to interrupt long periods of exhausting behavior. No ill-effects traceable to its use have been encountered, and it is considered a valuable and safe procedure, not only alleviating mental symptoms but also indirectly benefiting the tuberculosis. Close[2] recommends electric shock in acute psychotic illnesses with associated tuberculosis if delaying this treatment would reduce the possibilities of a good prognosis in the mental illness. He also recommends its use whenever there is a possibility of alleviating symptoms that interfere with the treatment of tuberculosis—that is, gaining the co-operation of the patient in obtaining proper nourishment, bed rest, collapse therapy or chest surgery.

Prefrontal lobotomy is considered a safe procedure for controlling behavior that interferes with the progress of the tuberculosis treatment but has been employed in only 1 case here. Lambriott, Washington and Bozalias[3] recommend shock treatment and prefrontal leukotomy in an effort to improve the mental status in selected cases.

Bedford Veterans Administration Hospital was one of the early hospitals to use streptomycin, at first in a dosage of 1 or 2 gm. daily, for periods of forty-two, ninety or one hundred and twenty days. At present it is being given as 1 gm. twice weekly combined with PAS, 12 gm. daily, and also with isoniazid, 300 mg. daily, over six, twelve and eighteen months and even

longer. More than 90 per cent of the patients treated in the Tuberculosis Unit have received one or more courses of chemotherapy.

Education

Patients, personnel, volunteer workers and visitors are indoctrinated regarding the sanitary precautions employed in the Tuberculosis Unit. Nurses and psychiatric aides are given special instructions in the entire control program and taught the details of care and treatment. Both group and individual instruction is given by the Tuberculosis Unit physician and by nurses who have had special training in the care of tuberculous patients with mental disease.

Table 1 shows the results of different types of chemotherapy used. Only patients with positive bacillary findings were included except for Group 6, many of whom had had sputum conversion as the result of previous chemotherapy before they were started on streptomycin and isoniazid.

Good results were expected in the cases in Group 1 because in 77 per cent the disease was minimal, and in the remainder it was moderately advanced.

In Group 2 50 per cent showed clinical improvement and 50 per cent x-ray evidence of regression. Many patients subsequently relapsed, and many cases became streptomycin resistant.

In Group 3 the results were fair but inferior to those with other forms of chemotherapy. PAS is no longer used alone.

Cases in Group 4 and in Group 6 were similar in severity in that they were mostly far advanced, had resisted previous courses of chemotherapy and were of poor prognosis. Comparison of the two regimens shows that the former was much more effective in producing x-ray evidence of regression but less effective in causing clinical improvement. There were fewer reacti-

Table 1. *Results of Treatment of Neuropsychiatric Patients with Tuberculosis.*

Group	Type of Therapy	Stage of Disease	No. of Patients	Patients with Conversion of Sputum	Patients Showing Clinical Improvement	Patients Showing No Change Clinically
1	Bed rest alone, for 3 mo. to 4 yr. (Average 18 mo.)	Minimal	10	9	2	8
		Moderately advanced	3	2	0	3
	Totals		13	11(85%)	2(15%)	11(85%)
2	Streptomycin 1-2 gm. daily, for 42-120 days	Moderately advanced	6	3	4	0
		Far advanced	14	4	6	3
	Totals		20	7(35%)	10(50%)	3(15%)
3	PAS, 12 gm. daily, for 90-180 days	Minimal	1	1	1	0
		Moderately advanced	5	3	2	3
		Far advanced	9	2	3	5
	Totals		15	6(40%)	6(40%)	8(53%)
4	Streptomycin, 1 gm. twice weekly, combined with PAS, 12 gm. daily, for 6-12 mo.	Minimal	8	8	5	3
		Moderately advanced	10	7	5	4
		Far advanced	9	4	4	5
	Totals		27	19(70%)	14(52%)	12(44%)
5	Isoniazid, 150 mg. daily for 2 mo. & 300 mg. daily for 2 mo. (total of 120 days)	Moderately advanced	2	1	0	2
		Far advanced	8	2	2	5
	Totals		10	3(30%)	2(20%)	7(70%)
6	Streptomycin, 1 gm. twice a week & isoniazid, 300 mg. daily for 6 mo.	Minimal	4	1	4	0
		Moderately advanced	4	2	4	0
		Far advanced	6	3	6	0
	Totals		14	6(43%)	14(100%)	0
	Grand Totals		99	52(52%)	48(49%)	41(41%)

vations in Group 4 than in Groups 1, 2 and 3, but not enough time has elapsed to determine the percentage of reactivations in Group 6.

PAS offers some difficulties in administration because of its undesirable taste and its tendency to produce nausea, vomiting and diarrhea whereas isoniazid has none of these undesirable effects. Both PAS and isoniazid are being used singly or together in combination with 1 gm. of streptomycin twice weekly and, when used in combinations, increase the antimicrobial effect of the drugs and delay resistance; in some cases, even after sensitivity tests have shown resistance to these drugs, clinical and x-ray evidence of improvement has been observed.

TABLE 1 *(Concluded).*

GROUP	PATIENTS APPEARING WORSE	DEATHS	PATIENTS WITH X-RAY SIGNS OF REGRESSION	PATIENTS SHOWING NO CHANGE ON X-RAY STUDY	PATIENTS SHOWING PROGRESSION	COMMENT
1	0	0	6	3	1	Mostly minimal cases; most cases asymptomatic before treatment.
	0	0	2	1	0	
	0	0	8(62%)	4(30%)	1(8%)	
2	1	1	4	0	2	Mostly far advanced cases; patients seriously ill.
	0	5	6	1	7	
	1(5%)	6(30%)	10(50%)	1(5%)	9(45%)	
3	0	0	1	0	0	Mostly moderately & far advanced cases
	0	0	2	1	2	
	1	0	3	4	2	
	1(7%)	0	6(40%)	5(33%)	4(27%)	
4	0	0	8	0	0	Best x-ray results obtained by this type of therapy
	1	0	9	1	0	
	0	0	5	2	2	
	1(4%)	0	22(81%)	3(11%)	2(8%)	
5						All cases resistant to streptomycin; all failures in previous types of treatment.
	0	0	0	1	1	
	1	0	1	2	5	
	1(10%)	0	1(10%)	3(30%)	6(60%)	
6	0	0	3	0	1	Disease had existed for over 3 yr. in all cases: some resistant to streptomycin; sputum negative in many cases before this course of treatment was started.
	0	0	4	0	0	
	0	0	2	3	1	
	0	0	9(64¼%)	3(21½%)	2(14½%)	
	4(4%)	6(6%)	56(57%)	19(19%)	24(24%)	

The results of chemotherapy are similar to those in tuberculosis hospitals all over the country as reported quarterly by the Veterans Administration, Army and Navy study. In brief, 1 gm. of streptomycin twice weekly, combined with 12 gm. of PAS daily, provided the most effective treatment of tuberculosis until the discovery of isoniazid. Combined with streptomycin, both PAS and isoniazid can be used over long periods (a year or two or longer), with few toxic effects. This therapy can be relied on, in a high percentage of cases, to convert the sputum from positive to negative, to show regression in x-ray films, to cause clinical improvement and, in many cases, to produce inactive disease. PAS and isoniazid are considered of about equal value when used in combination with streptomycin. Both have to a considerable extent replaced collapse therapy and in many cases have eliminated the need for chest surgery. Isoniazid has the advantage of being more easily taken because it has no disagreeable side effects.

Patients contemplated for chest surgery are given careful consideration regarding probable postoperative behavior, and a conservative policy has been observed in the selection of cases. Nevertheless, when operation

has been definitely indicated, it has been denied in only a few cases.

Pneumoperitoneum is a much safer form of treatment than pneumothorax, which is usually more effective, however, and is still employed in carefully selected cases. During the past few years chemotherapy has displaced all forms of temporary collapse procedures to a great extent.

Women's Building

This building has unwittingly served as an experiment to test not only the value of the tuberculosis control program but also the generally accepted view that the disease is usually spread by means of continuous rather than by occasional contact. The Women's Building of 80 beds, located a quarter of a mile from the other hospital buildings, is equipped with its own kitchen, dining room, dental clinic and recreational facilities.

This building was first opened in July, 1947, which was after the program had been instituted, and from the beginning, the methods to control the spread of tuberculosis were rigidly enforced. The few patients with active disease discovered at the time of admission have been transferred immediately to hospitals equipped to care for tuberculosis complicating neuropsychiatric disease in women, because such facilities have not been available here.

Although contact of female patients with the main building has been limited, it is fair to assume that occasional visits to the X-Ray Department, to the Infirmary in case of serious illness and to the main recreational buildings for a few diversional activities, as well as visits from relatives, have permitted exposure to tuberculosis.

From the beginning the building has remained free from tuberculosis, suggesting that the control program is sound and confirming the views already held that the disease is more frequently transmitted by continued direct exposure than by occasional or indirect contact.

Discussion

Table 2 shows the number of new cases of active tuberculosis discovered on Bedford surveys as compared with surveys in other places. This table does not include reactivated cases or those in which the diagnosis was made before admission. Also, the approximate proportion of cases to the total patient population of the hospital is given.

The city surveys were conducted on patients who had never been surveyed before, whereas the Bedford and Ontario surveys had been conducted yearly. Consequently, in the Bedford and Ontario surveys, the incidence of new cases would be expected to be smaller. However, when it is considered that tuberculosis is more prevalent in mental hospitals than in most other communities, the incidence of 0.11 per cent at Bedford Veterans Administration Hospital in 1952 (Table 2) is low in comparison with the approximate figure of 0.10 per cent expected in x-ray surveys of any large city.

Table 2. *New Cases of Tuberculosis Discovered in Chest X-Ray Surveys.*

Survey	Year	No. of Persons Examined	Type of Population Surveyed	New Cases Discovered	
				Number	Percentage*
Veterans Administration Hospital, Bedford, Mass.	1950 1951 1952	1,803	Mental patients	9 6 2	0.49 0.33 0.11
Ontario Mental Hospital[4]	1950	18,276	Mental patients	40	0.22
Harvard Public Health Chest Clinic[5]	1947–50	30,519	Medical students, nurses and other hospital personnel	72	0.24
City of Boston[6]	1949	343,000	General population	247	0.07
City of Baltimore[7]	1946	48,000	General population	292	0.60

*These figures are to be compared with expected incidence of tuberculosis in general population of any large city, which is estimated at 0.10 per cent.[8]

Summary and Conclusions

Methods employed at Bedford to control the spread of tuberculosis are outlined, problems encountered in the diagnosis and treatment of psychotic patients with tuberculosis discussed, and means of handling these problems without fundamentally changing established procedure in diagnosis and treatment described. The value of methods and agents generally employed in the control and treatment of the disease is briefly considered.

Control depends largely on periodic chest x-ray examinations and prompt segregation of active cases.

Diagnosis is accomplished principally by x-ray and laboratory methods, and detection of active disease must be accomplished without the help of subjective symptoms because they are concealed, unreliable or misinterpreted.

Treatment requires prompt application of bed rest and chemotherapy, as well as judicious use of collapse therapy and chest surgery. Electric shock, lobotomy, wet packs and occupational therapy are valuable adjuncts to treatment, and the intelligent efforts of Tuberculosis Unit personnel to induce patients to accept nourishment, medication and bed rest are indispensable.

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STUDIES OF RED-CELL VOLUME AND TURNOVER USING RADIOCHROMIUM*

Description of a New "Closed" Method of Red-Cell-Volume Measurement

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THE successful management of many clinical problems depends on information regarding the total volume of the mass of red cells in the body. The concentration of these cells in the peripheral blood is widely used as an index of total volume. The value of this determination depends on the accuracy with which it measures the over-all distribution of cells and plasma in the circulation. Changes in the hematocrit percentage of the peripheral blood can only reflect alterations in the size of the red-cell mass if the plasma volume remains constant. Keith et al.[1] showed in 1921 that the ratio of cells to plasma is not the same throughout the circulation; they also found that the blood volume may be altered by disease.

Dissatisfaction with concentration studies has stimulated the introduction of methods to measure the total mass of body constituents,[2] most of which are based on the principle of isotope dilution.[3] Radioactive chromium was first applied to the determination of red-cell volume by Sterling and Gray[4] in 1950. Their work showed that this isotope is taken up rapidly and becomes firmly bound by red cells in vitro.[5] These investigators believed that these favorable properties made radioactive chromium the best tracer available for studies of red-cell volume. The intracellular stability and convenient half life (twenty-six and a half days) presented by this isotope suggest that it might become of value clinically in long-term studies of red-cell turnover. The labeling procedure used by the original investigators was similar to that introduced in 1942 by Hevesy et al.[6] with radioactive phosphorus and necessitated open centrifugation, resuspension and washing of the patient's red cells. This handling of the blood takes time, increases the danger of pyrogenic contamination and may also damage the cells. This possibility of interference with red-cell viability naturally limits its application to studies of red-cell survival in the circulation.

Because of these considerations it seemed wise to make the labeling procedure simpler and more suitable for clinical use. This report describes the development of a method that reduces manipulation of the patient's blood to an absolute minimum consistent with labeling. The validity of such a technic in the determination of red-cell volume is examined in the human subject. The rate of disappearance of red cells labeled by this method has been studied in normal persons and is also reported.

Materials and Methods

The radioactive chromium used in this work was in the chromate form ($Na_2 Cr^{51} O_4$). Originally the tracer varied in specific activity between 150 and 1200 mc. per gram; recently, it has been obtainable with an activity as high as 2400 mc. per gram. Radioactivity was measured in Pyrex test tubes (10 by 1.2 cm.) with a well-type scintillation counter.‡ The coefficient of variation of multiplicates of between 1 and 2 cc. counted by this method was 0.4 per cent. Chromium concentrations were calculated from the activities of the samples by means of the known specific activity of the tracer. Heparin was the anticoagulant used in all studies. Hematocrits were measured in Wintrobe tubes centrifuged at an average of 2000 to 3000 revolutions per minute§ for fifty-five minutes. Readings were taken at the top of the red-cell column without any correction for trapped plasma. Plasma volumes were measured by the method of Gibson and Evans with T_{1824}.[7]

Studies of Uptake of Radioactive Chromium by Whole Blood

A series of incubation studies was undertaken as a basis for the use of red-cell tagging in whole blood. Fresh blood was incubated for periods of up to four hours at both room temperature and 37°C. with con-

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‡Obtainable from W. S. Macdonald Company, Cambridge, Massachusetts.

§Mean acceleration, 1800 g.

centrations of chromium ranging from 5 to 200 microgm. Samples were removed at intervals for the calculation of hematocrit, whole-blood and plasma activity. From these data the percentage distribution under varying conditions of chromium concentration, temperature and time of incubation was determined.

The results (Fig. 1 and 2) showed an initially rapid uptake in the cells followed by a slower rate of incorporation. When uptake by the red cells had ceased, approximately 10 per cent of the added tracer remained in the plasma. This distribution was unaffected by either further incubation or the addition of fresh red cells if the pH was not allowed to rise. The labeling process was accelerated when the temperature was raised from 24 to 37°C. Some hemolysis was found when incubation was continued for longer than two hours at 37°C. with concentrations of radiochromium greater than 30 microgm. per cubic centimeter of red blood cells. These changes occurred despite the maintenance of a normal blood sugar during the investigations.

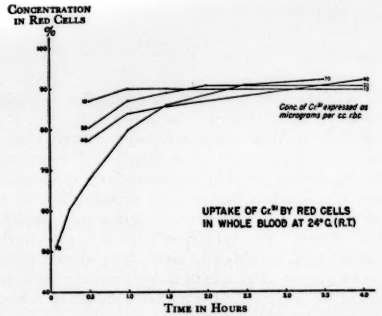
Concentration in Red Cells
%
Conc. of Cr51 expressed as micrograms per cc. rbc.
UPTAKE OF Cr51 BY RED CELLS IN WHOLE BLOOD AT 24°C. (R.T.)
Time in Hours

FIGURE 1. *Incorporation of Radiochromium into Erythrocytes of Whole Blood in Vitro at Room Temperature. Variations in total chromium concentration from 10 to 70 microgm. per cubic centimeter of erythrocytes introduce only minor differences in total uptake; the lower concentrations achieve equilibrium more rapidly. About 90 per cent of the added chromium appears in the cells, and the remainder becomes "unavailable" for red-cell tagging.*

The activity that remained in the plasma after maximal uptake by the red cells was apparently due to the presence of protein, as shown by the fact that red cells resuspended in a "protein-free" buffer* solution were able to take up 98 per cent of the added tracer (Fig. 3). The nature of the radiochromium that remained in the plasma unavailable to red cells was then investigated. Samples of this plasma were subjected to both dialysis through a cellophane membrane against a buffer solution for twenty-four hours and passage over an anion exchange resin.† Approximately a third of the plasma chromate activity could be removed by these measures. Thus, although not taken up by red cells, this radiochromium was not all strongly bound to plasma protein. When incubation took place at pH 7.7 the final state of distribution was unaffected by a fall to pH 7.1. However, the opposite was not true. At pH 7.1 twice as much activity remained bound to protein. A change in the pH to 7.7 after incubation led to a drop of 50 per cent in the protein-bound fraction. The radiochromium released was available for red-cell uptake. This action of hydrogen ion concentration on the protein-bound fraction is similar to its effect on the binding of other anions.[5]

To obtain accurate measurements of red-cell volume with the use of fresh whole blood it is essential that any radiochromium that has not been taken up by red cells before introduction into the patient should not enter his red cells after injection. To avoid the necessity of washing the cells free of plasma activity before reinjection various methods of preventing further uptake by red cells were explored.

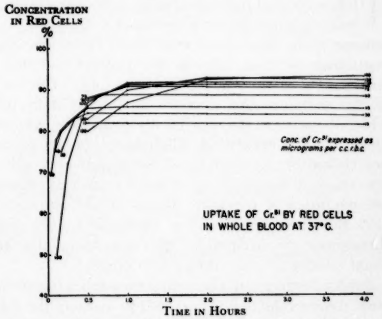
Concentration in Red Cells
%
Conc. of Cr51 expressed as micrograms per c.c. rbc.
UPTAKE OF Cr51 BY RED CELLS IN WHOLE BLOOD AT 37°C.
Time in Hours

FIGURE 2. *Incorporation of Radiochromium into Erythrocytes of Whole Blood in Vitro at 37°C. The higher chromium concentrations (over 60 microgm. per cubic centimeter of erythrocytes) show a somewhat higher intracellular fraction than the lower ones. The uptake throughout is more rapid than at room temperature (Fig. 1) and is essentially complete (90 per cent in cells) at thirty minutes.*

The persistence of dialyzable activity in the plasma after the completion of red-cell uptake suggested that some of the radiochromium had been converted to a form (?trivalent) that was unable to penetrate the red-cell membrane. Merely awaiting the completion of red-cell uptake and then depending on the unavailability of the remaining plasma activity was tried. This technic, unfortunately, requires careful pH control to guard against changes in the plasma binding of chromate ion.

*This buffer was phosphate bicarbonate solution containing the same cation concentration as plasma and equilibrated to pH 7.4 with 10 per cent carbon dioxide. The suspensions always contained some protein since complete removal of plasma by washing caused hemolysis of the cells on subsequent incubation.

†Nalco S. B. R., supplied by National Aluminate Company, Chicago.

Since sodium chromate is an oxidizing agent a logical step seemed to be its reduction to trivalent chromium. On this hypothesis, 50 mg. of ascorbic acid (a natural, strong reducing agent) was added to as much as 500 microgm. of radioactive sodium chromate. The uptake of this tracer by red cells both in vitro and in vivo was prevented. This observation forms the basis for the ascorbic acid step in the closed technic.

Technic for Determination of Red-Cell Volume

With the use of ascorbic acid a series of measurements of red-cell volume were carried out. In these studies the chromium concentration during incubation was kept as low as possible, accelerating the uptake of chromium and reducing the danger of toxicity. In some of the early determinations the patient's blood was incubated at 37°C. to hasten uptake. (With the very high assay material now available the use of this high-temperature step is unnecessary.) In most cases

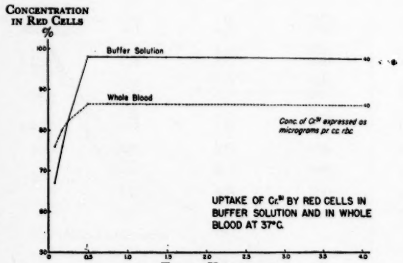

Figure 3. *Incorporation of Radiochromium into Erythrocytes of Whole Blood at 37°C. as Contrasted with Erythrocytes in Protein-Free Buffer Solution.*

In contrast to the uptake in whole blood of 85 to 90 per cent (see also Fig. 1 and 2) the protein-free buffer permits 98 per cent incorporation of the tracer into cells.

the concentration of chromium to which the red cells were exposed was below 10 microgm. per cubic centimeter of red blood cells. This low concentration is achieved by the use of between 40 and 50 cc. of the patient's blood and incubation with highly active radiochromium. A modification of the Walter[9] plastic transfusion unit (Fig. 4) was used in all cases.* With this apparatus instead of a syringe the risk of contaminating and damaging the blood while it is outside the body is materially reduced. This unit is convenient to use and can be discarded at the completion of the study, avoiding radioactive contamination of sampling syringes and other laboratory equipment.

In the performance of a volume study 75 to 100 μ of radioactive sodium chromate in about 5 cc. of saline solution with 0.5 cc. of heparin is injected through the rubber cuff in the donor tube of the equipment shown in Figure 4 after the air has been evacuated from the bag. The solution is autoclaved before injection. The bag is sterile. The bag, whose capacity is about 50 cc., is then filled with blood from the patient by venipuncture, and the donor tube is tied or clipped. The unit is shaken intermittently at room temperature for thirty to forty minutes. With the radiochromium concentrations used the rapid phase of uptake ensures almost complete uptake in this period; 50 mg. of ascorbic acid† is injected through the rubber cuff of the recipient tube. In repeated experiments, with the concentrations encountered, this amount of reducing agent more than prevented any further transfer of the plasma activity to the red cells. The plastic bag unit is then weighed,

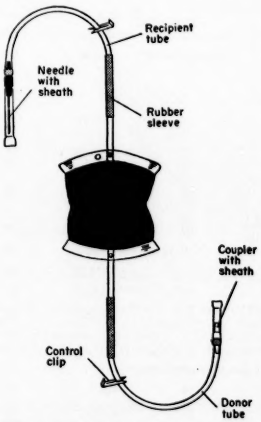

Figure 4. *Plastic Bag for Use in Closed Chromate Method of Measuring Red-Cell Volume (the Small Steel Ball, Which Is Shown in both "Donor" and "Recipient" Positions in the Tubing at the Two Ends of the Bag, is in the Upper Position during Collection of the Blood and Is Squeezed Back into the Lower Position during Delivery).*

The bag is filled with blood via the donor tube after it has been emptied of air, and the tracer, as well as a small amount of heparin, is added through the rubber cuff. The bag is shaken at room temperature for thirty to forty minutes; ascorbic acid is then added to stop red-cell uptake, and the blood injected via the recipient tube. A small sample is saved for counting. The injected volume is determined by weight change and specific gravity.

and all but 5 cc. of the blood is injected into the patient by a combination of gravity and manual pressure.‡ A dry needle is employed for the infusion. The amount of labeled blood injected is determined to the nearest milligram by reweighing of the equipment on a suitable scale. Measurements of specific gravity (by

*Obtainable from the Fenwal Laboratories, Ashland, Massachusetts.

†1 cc. of the Sharp and Dohme ampoule of ascorbic acid (intravenous) is used, containing 2 per cent bisulfite. Both chemicals are reducing agents.

‡The small steel ball that occludes the outlet tube is squeezed back into the bag and fixed securely at the opposite end of the bag for injection of tagged blood into the patient.

the method of Philips et al.[10]), hematocrit and radioactivity of whole blood and plasma are made on this retained sample of blood. The distribution and size of the injected dose can thus be established.

Equilibration samples of blood are drawn from the patient into heparin twenty and forty minutes after injection. The hematocrit is measured in each sample. Enough of this blood to contain approximately 2 cc. of cells (4 to 8 cc. of whole blood, depending on the hematocrit) is carefully pipetted into counting tubes and centrifuged. The supernatant plasma is removed, and the cells are counted. Both cells and plasma may be diluted appropriately, depending on the total activity desired for counting.*

mum difference in these studies was 9 per cent (Tables 1 and 2). The average of 14 determinations in 8 normal men was 29.5 cc. per kilogram of body weight (Table 1). In 1 normal person the red-cell volume was determined by the Ashby method[11] on the same day as a chromium determination. The agreement between the two methods was within 1 per cent.

Twenty synchromous studies of radiochromium red-cell volume and Evans-blue-dye plasma volume were made on 14 surgical patients (Table 2). All the duplicate measurements followed operation or transfusion except for one reproducibility determination. The red-cell volume calculated from the plasma volume and peripheral hematocrit was greater than the

TABLE 1. *Differences in Red-Cell Volumes of Normal Subjects.*

SUBJECT	DETERMINATION NO.	DATE	AGE	WEIGHT	RED-CELL VOLUME	RED-CELL VOLUME/KG. OF BODY WEIGHT	VENOUS HEMATOCRIT	DIFFERENCE IN DUPLICATES
Normal men:			yr.	kg.	cc.	cc.	%	%
J. G.	1	11-6-52	32	81.8	2516	30.7	47.8	
	33	3-10-53	32	80.3	2450	30.6	47.0	−2.6
R. M.	13	12-23-52	23	74.45	2068	28.8	45.7	
	31	4-1-53	23	76.6	1948	25.4	44.1	−5.8
M. A.	14	12-31-52	24	70.0	2100	30.0	52.0	
	38	4-8-53	24	70.5	2290	32.5	50.0	+9.0
L. O.	39	4-10-53	23	68.2	2060	29.4	48.5	
	40	4-11-53	23	68.4	1935	28.3	51.0	−6.0
R. S.	9	12-9-52	28	66.8	2037	29.9	48.0	
F. T.	11	12-15-52	45	93.0	2743	29.5	54.0	
C. A.	15	1-6-53	57	69.2	1912	27.6	52.3	
A. S.	41	4-21-53	49	78.2	2425	31.0	47.0	
							Mean=29.5 (±0.58) S.D.	
Normal man 7 days after phlebotomy:								
L. Y.	34	4-3-53	23	67.3	1710	25.5	45.5	
L. Y.	35	4-4-53	23	67.3	1760	26.2	43.5	±2.9

RESULTS

A total of 34 determinations were undertaken. Duplicate measurements of red-cell volume were made in 5 normal men and in 1 woman suffering from hypochromic anemia. In 3 of the normal subjects the interval between determinations was three months; in the remainder it was twenty-four hours. The maxi-

*Calculation is made as follows:

$$\text{Volume of blood injected (V)} = \frac{\text{weight of blood injected}}{\text{specific gravity}}$$

$$\text{Total whole-blood counts injected (T)} = \text{counts per cubic centimeter of whole blood} \times V$$

$$\text{Total plasma counts injected (P)} = \frac{\text{counts per cubic centimeter of plasma injected} \times V \times (100 - \text{hematocrit}^1)}{100}$$

$$\text{Counts injected in red cells (C)} = T - P.$$

$$\text{Counts per cubic centimeter of circulating red cells (R)} = \frac{\text{mean counts in sample}}{\text{volume of sample}} \times \frac{1}{\text{hematocrit}^2 \text{ (mean)}}$$

$$\text{Red-cell volume} = \frac{(C)}{(R)} \text{ cc.}$$

Hematocrit[1] = hematocrit of injected blood from bag.
Hematocrit[2] = hematocrit of blood sample from patient.

radiochromium red-cell volume in all cases except 1.

The mean value of the ratio of radiochromium to dye red-cell volume was 0.81±0.03 (S.D.). Similarly the total body hematocrit calculated from the ratio of radiochromium red-cell volume to that plus dye plasma volume was less than the venous hematocrit.

The mean value for the ratio of total body hematocrit to venous hematocrit was 0.88±0.02 (S.D.).

DISAPPEARANCE OF CIRCULATING RED CELLS AND PLASMA Cr^{51}

The rate at which labeled red cells disappear† from the circulation after injection depends on a number of factors. Apart from the viability characteristics of the red cells labeled, the degree of leakage of chromium from the cells, the possibility of chromium reutilization and any damage due to the labeling procedure itself could affect the observed loss. Before the study of disappearance rates in vivo some in vitro experi-

†"Disappearance" means the decline in total red-cell radiochromium activity per unit of red cells, in peripheral samples.

ments were carried out in an attempt to assess the magnitude of these influences.

The possibility of reincorporation of the radioactive chromium by other cells after destruction of the initially labeled cells was explored by incubation of fresh cells at 37°C. in a hemolysate prepared from chromated cells. No uptake could be detected. A similar negative result was obtained when a labeled hemolysate was injected intravenously into a dog. The circulating red-cell mass did not take up chromium.

To investigate the likelihood of chronic leakage of the tracer, labeled red cells were left at room temperature for two days and at 4°C. for three weeks. In the absence of hemolysis not more than 5 per cent of the activity left the red cells and appeared in the plasma under these conditions.

In the determinations of volume described above, the red-cell activities remained constant during the first forty minutes after injection, with a variation around the mean of 1.3 per cent.

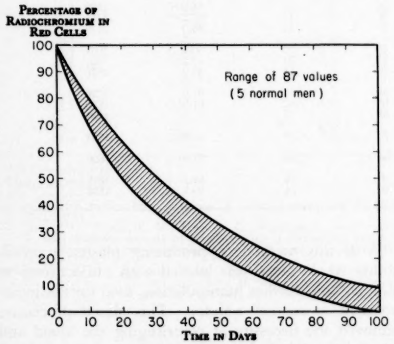

FIGURE 5. *Survival of Chromate Tagging of the Red Cell. The initial tracer activity is taken as 100 per cent. There is a biologic-decay slope leading to complete disappearance of the activity in about a hundred days. The subjects were normal young adult males. The configuration of the curve suggests but does not prove that the decline in erythrocyte chromate activity is a function of red-cell survival.*

In 5 normal men the red-cell unit activity was followed for eighty to a hundred days. The interval readings were corrected for decay and expressed as a percentage of the original activity concentration. The results (Fig. 5 and 6) indicated that radiochromium left the red-cell mass exponentially with a half life of twenty-eight days. The plasma radiochromium injected in the forty red-cell-volume determinations varied between 5 and 30 per cent of the total injected activity (mean, 14 per cent). In these cases the plasma activity fell in twenty-four hours to between 7 and 27 per cent of its original value. During this period an amount of radioactivity equal to half the injected plasma dose could be recovered from the urine.

Discussion

These incubation studies confirm and extend the original observations of Sterling and Gray.[4] However, the uptake of chromium by red cells was found to be biphasic and not a single exponential process. The inhibition of chromate uptake by ascorbic acid ob-

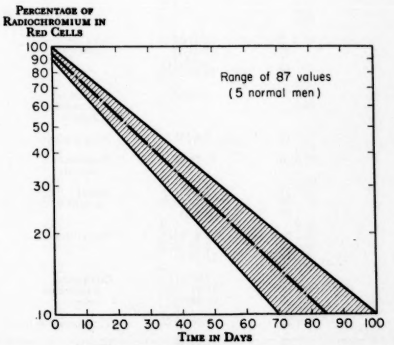

FIGURE 6. *Survival of Chromate Tagging Plotted on Semi-Log Co-ordinates.*

The linear slope suggests that a single exponential will express the decline in activity as a function of time. The biologic half life is twenty-eight days. The usefulness of such data in the study of anemia is suggested.

served supports the original concept that a reducing agent prevents the leakage of chromium from the red cell.[5] Reproducible measurements of red-cell volume could be obtained by the use of a simplified procedure for labeling the cells with chromium. One can ascertain the accuracy of these determinations only by comparing the results with those obtained under similar conditions with an alternative, accepted method. Radioactive iron, because of the integral nature of its label, is the most suitable reference standard. In these studies the mean red-cell volume of normal men was found to be 29.5 cc. per kilogram of body weight. This figure agrees with that of 29.7 cc. with the use of radioactive iron[12] and is slightly below that of 31.8 cc. reported by Sterling and Gray[4] with radiochromium. The T_{1824} measurements of plasma volume performed on hospital patients synchronously with the determinations of red-cell volume enable an indirect comparison with previous work. Thus, the values of 0.81 and 0.88 for the mean of the ratios of total body to venous hematocrit and of radiochromium to dye red-cell volume are almost identical with those of 0.81 and 0.89 found in 25 patients by means of radioactive iron and Evans-blue dye.[13] The rate at

which radioactivity leaves the red-cell mass was reproducible in normal persons even though in 1 case, J.G., the concentration of chromium for incubation was 30 microgm. per cubic centimeter of red cells. Chromium could still be detected a hundred days after its introduction into the body. This approaches the expected survival time for red cells (a hundred to a hundred and twenty days).[14] These observations suggest that the disappearance of radiochromium is intimately related to the life of the red cell itself. However, studies with the Ashby isoagglutination method have shown that red cells are removed from the circulation in a linear fashion, with a half life of fifty to sixty days.[14] The explanation for this discrepancy must await further investigations, which will also decide the real value of this isotope in the study of anemia.

Table 2. *Blood-Volume Data by "Closed Chromate Method" and Dye in a Variety of Pathologic States.*

Determination No.	Date	Diagnosis	Sex	Age	Weight	Red-Cell Volume
				yr.	kg.	cc.
2	11-11-52	Myeloid metaplasia	M	65	74.6	1269
30	3-31-53		M	66	65.2	1420
7	11-9-52(1)		M	72	70.1	868
16	12-10-52(2)		M	72	68.9	2971
26	2-27-53	Congenital hemolytic anemia	M	37	66.0	1727
19	2-4-53	Polycythemia	M	65	75.0	2556
6	11-19-52	Pulmonary stenosis	M	48	54.5	1888
17	1-7-53(1)	Mitral insufficiency	M	43	66.0	2129
18	1-13-53(2)		M	43	65.2	1311
21	2-2-53		F	21	46.0	2170
20	1-6-53(1)	Mitral stenosis	F	31	46.0	1057
25	2-19-53(2)		F	31	45.5	665
12	12-19-52		F	54	43.0	1670
8	12-6-52(1)	Compound fracture of femur	M	52	91.0	2226
10	12-11-52(2)		M	52	91.0	1858
5	11-18-52		M	17	52.3	1634
22	2-16-53	Thyrotoxicosis	F	39	50.0	1897
3	11-13-52	Hernia	M	64	71.9	1600
36	4-3-53(1)	Hypochromic anemia	F	24	59.1	1215
37	4-6-53(2)		F	24	59.1	1210

Summary

The effect of concentration, time, temperature, plasma and pH on the uptake of radioactive chromium by red cells in whole blood is discussed. Red cells in whole blood were able to take up approximately 90 per cent of added radiochromium in a time that varied with the dosage and temperature of incubation. Once in the red cell the chromium did not leave and was not reutilized after destruction of the cell.

The plasma radiochromium not taken up by red cells after the development of equilibrium remained unavailable to red cells as long as the pH was not allowed to rise. It consisted of protein-bound and diffusible fractions.

Reduction of radiochromium with ascorbic acid stopped red-cell uptake regardless of time of incubation or pH.

With this method of producing plasma unavailability whole blood was labeled with radiochromium and, without further manipulation, used for the measurement of red-cell volume. This closed procedure removed the necessity of centrifuging the blood and greatly simplified the determination of the red-cell volume in surgical patients.

Thirty-two determinations were carried out in normal subjects and hospitalized patients, a closed plastic-bag technic being utilized. Red-cell volumes were reproducible within 9 per cent and, when compared with Evans-blue-dye volumes, gave results consistent with those previously obtained with radioactive iron.

The disappearance of radiochromium from the red-cell mass in 5 subjects was exponential with a half life of twenty-eight days.

I am indebted to Drs. Carl W. Walter, John Gibson, Searle Rees and Graham Wilson for helpful suggestions, Dr. A. K. Solomon for the use of the scintillation counter, Dr. Francis D. Moore for support and guidance, and Miss Margaret Ball for help in the Evans-blue-dye determinations.

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TABLE 2 *(Concluded).*

Red-Cell Volume/Kg. of Body Weight	Plasma Volume	Radiochromium Red-Cell Volume / Red-Cell Volume (Dye)*	Hematocrit	Total Body Hematocrit	Total Body Hematocrit / Venous Hematocrit†
cc.	*cc.*		%	%	
17.0	6600	0.87	18.0	16.1	0.89
21.8	3800	0.74	33.5	27.2	0.81
12.7	4100	1.05	16.7	17.4	1.04
43.2	4100	0.77	48.5	42.0	0.86
26.1	3300	0.66	40.3	34.4	0.85
34.0	3230	0.73	52.0	44.2	0.85
34.6	3300	0.83	40.8	36.4	0.89
32.3	2830	0.85	47.0	42.9	0.91
20.1	3050	0.68	38.6	30.0	0.77
43.7	2560	0.89	48.6	45.9	0.94
23.0	1940	0.76	42.0	35.2	0.84
14.6	1940	0.65	35.0	25.5	0.72
38.8	1980	0.82	50.5	45.6	0.90
24.4	3300	0.83	43.7	40.3	0.92
20.4	4300	0.79	35.2	30.1	0.85
31.2	2730	0.79	43.0	37.4	0.87
37.8	2600	0.89	44.2	42.1	0.95
22.2	2440	0.92	41.6	39.6	0.95
20.5	2500	0.81	37.5	32.7	0.87
20.4	2800	0.72	37.4	30.0	0.80

*Mean = 0.81±0.03.
†Mean = 0.88±0.02.

ABSENCE OF SERUM GAMMA GLOBULINS IN AN ADULT*

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BOSTON

THE syndrome of low serum gamma globulin in the presence of relatively normal quantities of the other protein factors has recently been described in children, but has not heretofore been observed in adults. The first case of "agammaglobulinemia" was reported by Bruton[1] in a boy who, between the ages of four and a half and eight years, had 18 bouts of sepsis with 8 different types of pneumococci isolated, 5 episodes of otitis media, and 3 attacks of epidemic parotitis. Prophylactic antibacterial therapy was not always successful in preventing reinfection. After autogenous pneumococcal vaccine, typhoid vaccine and diphtheria immunization, no circulating antibodies could be detected. Moreover, no complement-fixing antibodies were present in the serum twenty-two days after the third episode of epidemic parotitis. A deficiency in serum gamma globulin was demonstrated, and the recurrent infections were controlled by repeated injections of gamma globulin.[2]

Nine other patients with this syndrome have since been described,[3] all having recurrent infections that were most frequently caused by pneumococci, menin-

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gococci, staphylococci, or *Haemophilus influenzae*.[2,3] Previously, the entity has not been seen in a female.

Case Report

A 39-year-old housewife (para 2, gravida 4), who had been born in Massachusetts, entered this hospital in September, 1953, with the complaint of cough of many years' duration. Frequent colds accompanied by bronchitis, particularly during the winter months, had begun early in childhood (Fig. 1). By the age of 17 a chronic cough, worse in the morning, had appeared. At 23 anorexia, weakness, weight loss and watery diarrhea, with foamy, foul smelling stools, led to an ischiorectal abscess requiring surgical drainage. By the age of 30 the diarrhea was limited to several short bouts each year whereas the cough had become productive of yellow-green sputum. In 1947 3 upper respiratory infections were treated with penicillin, and 1 bout of bilateral otitis media was treated with a sulfonamide. In December, 1948, at the age of 31, the patient was hospitalized for extensive study.*

Physical examination revealed a thin, chronically ill woman with a diffuse increase in skin pigmentation. Crepitant rales at the base of the right lung constituted the only important physical abnormality.

Significant laboratory findings included a microcytic

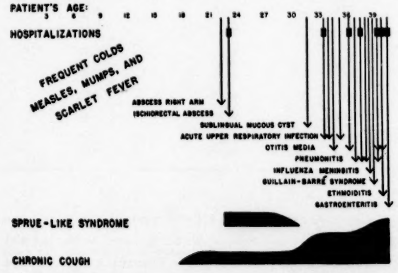

FIGURE 1. *Various Infections and Hospitalizations in a Patient with Agammaglobulinemia.*

normochromic anemia (hemoglobin of 10.5 gm. per 100 cc.), a corrected sedimentation rate of 25 mm. per hour (Wintrobe method), normal respiratory flora, and a total serum protein of 4.8 gm. per 100 cc. (albumin of 3.8 and globulin of 1.0 gm.). The calcium, phosphorus, chloride, sodium and prothrombin time were normal. The stools gave + to ++++ tests for mucus but contained no fat, parasites or blood. The oral glucose tolerance test was "flat." Bronchographic study demonstrated minimal dilatation of the posterior basal segments of both lower lobes. A gastrointestinal series showed segmentation, puddling and marginal irregularity of small-bowel loops.

Postural drainage, vitamin supplements, diet and aerosol penicillin effected moderate improvement in the bronchiectasis and sprue-like syndrome.

The patient did reasonably well until February, 1951, when a myringotomy was performed for an acute otitis media on the left that was later complicated by pneumonic consolidation of the posteroinferior segment of the left lower lobe. This cleared after penicillin therapy. In June severe pain in the left side of the chest and a temperature of 104°F. accompanied "small pulmonary infarcts" in both costophrenic sulci. On the assumption that these areas were the result of emboli, bilateral femoral-vein ligation was carried out and Dicumarol was given. In December severe pleuritic pain, infiltration of the right lung and a temperature of 105°F. recurred, without evidence of thrombophlebitis. Dicumarol was again administered.

*We are indebted to the Joseph H. Pratt Diagnostic Hospital for making available the clinical findings observed during this admission.

In June, 1952, an acute quadriplegia after an exacerbation of diarrhea responded promptly to 6.0 mg. of intravenous calcium gluconate.† At that time the serum calcium was 6.4 mg. per 100 cc. The spinal fluid was normal. Forty-eight hours later acute meningitis developed, with a temperature of 106.4°F., shaking chills and a stiff neck. A restudy of the spinal fluid showed 13,950 cells per cubic millimeter, with 93 per cent segmented forms, a sugar of 11 mg. and a protein of 196 mg. per 100 cc. and *H. influenzae* on culture. Streptomycin and sulfadiazine treatment induced a prompt recovery. Three weeks later the spinal fluid contained 198 cells per cubic millimeter and a normal sugar and protein. A.T. 10 and cortisone alleviated the gastrointestinal symptoms. At this time the total serum protein was 4.75 gm. and the serum calcium 10 mg. per 100 cc.

Four weeks after the onset of the meningitis pain in the lower back and weakness of the extremities developed. The spinal fluid was normal. Within 24 hours a rapidly progressive symmetrical ascending paralysis appeared, involving the legs, hips, abdominal and back musculature and then the upper extremities and the muscles of deglutition. Anisocoria, hyporeflexia, impairment of temperature perception, loss of vibratory sense in the right leg and a hyperesthesia of the right hemithorax were noted. At this time the spinal fluid contained 216 cells per cubic millimeter, with 28 per cent neutrophils, 72 per cent lymphocytes and a protein of 80 mg. per 100 cc.; 4 weeks later the count was 12 cells per cubic millimeter with a protein of 188 mg. per 100 cc. By November 1, 3 months after the onset of the myelitis, the cerebrospinal-fluid protein was 55 mg. per 100 cc.; sensory symptoms had disappeared, but paresis of the lower extremities persisted.

Between November, 1952, and April, 1953, there were repeated attacks of otitis media, pharyngitis and pneumonitis similar to those that had occurred earlier. The cough became intractable and was accompanied by a purulent bronchorrhea that responded poorly to antibiotic therapy. During hospitalization for the pulmonary difficulty in April a total serum protein of 3.8 gm. per 100 cc., with a globulin of 1.06 gm. led to the first suspicion of the syndrome of low gamma globulin. Lumbar puncture was normal. Because of severe motor weakness the patient was transferred to another hospital on April 13, for further evaluation and physiotherapy.‡

At this time skin pigmentation, rales at the lung bases, motor weakness of the right hand, bilateral interosseous muscle atrophy of the hands and flaccid paralysis of the lower extremities, with moderate muscular atrophy, were again noted. The hemoglobin was 13 gm. per 100 cc., with a direct eosinophil count of 176 per cubic millimeter and a total serum protein of 5.1 gm. per 100 cc. The calcium and phosphorus were normal. Intradermal tests with 1:1000 and 1:100 dilutions of Old Tuberculin were negative. *H. influenzae* was cultured from the sputum. An oral glucose tolerance test was "flat." Stool tryptic activity was normal. The vitamin A absorption was diminished. There was a threefold increase in stool fat on a controlled diet. The right half of the diaphragm was elevated, and bronchial markings were increased; thickened walls of the maxillary sinuses and obliterated ethmoid sinuses were also noted.

During the rehabilitation program in the hospital the ethmoiditis was treated successfully with penicillin and streptomycin but was complicated by otitis media on the left that was due to a *Micrococcus pyogenes* (var. *aureus*), which was treated with erythromycin. A week later bilateral otitis media necessitated myringotomy.

After discharge difficulty in raising bronchial secretions because of an ineffective cough and overflow bronchorrhea led to admission to this hospital on September 8 for study of the pulmonary disease.

Between hospitalizations on July 28 and August 28, the patient had received a 6-cc. injection (180 mg. per cubic centimeter) of gamma globulin. No change in her course was noted.

The family history was unremarkable. As a child she had had 1 attack each of measles, mumps and scarlet fever. An

†We are indebted to the Haverhill Municipal Hospital for making available the clinical findings described during this and the following admission.

‡We are indebted to the Children's Medical Center for making available the clinical findings observed during this admission.

apparently successful smallpox vaccination was performed before she started school. An appendectomy at 10 years of age was followed by a laparotomy for "lysis of adhesions" at the age of 17.

Physical examination showed a slight, deeply tanned, chronically ill woman. An ineffective, barely audible cough, productive of small amounts of watery, mucoid sputum, occurred on slight exertion and with conversation, which was carried on in gasps of 5 to 10 words. Reddened retracted tympanic membranes and a boggy nasal mucosa were noted. No lymph nodes could be felt, nor was the spleen palpable. The pharynx was clear. The respiratory movements were carried out largely with the upper accessory muscles of respiration. Moist rales and rhonchi were heard throughout both lung fields. There was weakness of the thenar and flexor muscles of the right hand and a flaccid paralysis of both legs and the lower trunk musculature. Sensory modalities were intact. Tendon reflexes were equal and hyperactive in the arms and absent in the legs. No plantar responses could be elicited.

The temperature, pulse and respirations were normal. The blood pressure was 105/70.

The hematocrit was 43 per cent, and the hemoglobin 13.4 gm. per 100 cc., with a mean corpuscular hemoglobin concentration of 31 per cent. The total protein was 4.7 gm. per 100 cc. (albumin of 4.1 gm. and globulin of 0.6 gm). The fasting blood sugar was 80 mg. per 100 cc., and the calcium 5.2 milliequiv. per liter.

Cultures of the sputum demonstrated alpha-hemolytic streptococci and *H. influenzae*. PPD tuberculin skin tests in 1st and 2nd strength were negative. Intradermal skin tests with bacterial antigens, prepared from alpha-hemolytic streptococci and *M. pyogenes* (var. *aureus*) were positive. Tests with beta-hemolytic streptococci and *Diplococcus pneumoniae* as antigens were negative. Vaccination with vaccinia caused an enormous swelling of the arm, with an area of necrosis 2 by 2 cm. that became maximal at 10 days and lasted for 6 weeks. Roentgenograms of the chest were similar to previous examinations. Pulmonary-function studies with the patient recumbent, as well as with the head lowered 35° to facilitate postural drainage of bronchial secretions, indicated decreased ventilatory capacity and diminished lung compliance without evidence of emphysema.

The patient's blood was Type B and Rh positive, of subtype Rh_1, probably homozygous. Anti-A isoagglutinin titers in saline solution were all negative. An electrophoretic analysis of the serum 3 weeks after the last injection of gamma globulin showed no gamma globulin peak. A quantitative immunochemical determination of the gamma globulin was 25 mg. per 100 cc., or approximately 0.5 per cent of the plasma proteins (normal, 14 per cent*).[4]

After discharge from the hospital the patient received 30 cc. of purified gamma globulin (0.1 gm. per kilogram of body weight) each month. Subjective improvement was not apparent until 48 hours after the 1st injection. There had been no acute infections up to the time of this writing. The chronic cough had become less productive — both tympanic membranes appeared normal, and a chronic tenosynovitis of the right wrist had cleared.

Isohemagglutinin titers in saline solution on serum samples from the patient's 2 sons were anti-A (1:64 and 1:256).

Discussion

This woman with the syndrome of low serum gamma globulin presented a clinical picture similar to that seen in children with this entity. The history of influenzal meningitis at the age of thirty-eight is unusual and suggests mechanisms that favor this disease in infants. Repeated infections of the lungs, pharynx, sinuses and middle ears are characteristic findings in children with low serum gamma globulin. Most children with this disease probably have not survived to reach adult life, and therefore its recognition in adults has been delayed.

*We are indebted to the laboratories of the Children's Medical Center for carrying out these procedures.

The half life of gamma globulin and of passively transferred antibodies in children with this condition is approximately twenty days,[2] which is within the normal range for children.[2] This finding suggests that the defect is a failure in globulin synthesis, either congenital in origin, as in hemophilia and afibrinogenemia, or acquired later in life, as Bruton et al.[2] thought was the situation in their initial patient. The parents and siblings in 2 cases possessed normal plasma proteins.[2] The 2 sons of the patient described above had quite normal serum protein components.

Replacement of gamma globulin requires approximately 0.1 gm. per kilogram of body weight to reach blood levels that appear to be adequate for the control of infection (100 to 150 mg. per 100 cc.).[3] Unfortunately, levels that do not approximate this are of little value.[3] In children this dose must be given every four to six weeks. In adults whose gamma globulin half life may be less[5] than that in children treatment may be needed more frequently.

The complexity of an electrophoretic or immunochemical study of plasma proteins limits their use to the research laboratory. It is possible, however, to screen a large number of suspected cases by the much simpler determination of isohemagglutinin titers; persons with a measurable titer do not have an absence of gamma globulin.[3] In the absence of isoagglutinins the suspected diagnosis may be confirmed by the quantitative determination of gamma globulin.

The syndrome in this adult patient so closely simulates the condition previously described in children that the diagnosis can be entertained on the clinical features. Absence of gamma globulins should be suspected in adults with multiple respiratory infections in association with other infections, and perhaps in sprue-like syndromes. Since the defect can apparently be corrected by replacement therapy, which limits disability and forestalls further complications resulting from various infections, diagnosis is of considerable importance.

Summary

The occurrence of a very low serum gamma globulin in a thirty-nine-year-old woman is described. Bronchiectasis and a sprue-like syndrome were the presenting features of this condition. Repeated infections including meningitis due to *Haemophilus influenzae* in the adult years and an ascending paraplegic myelitis followed by marked motor weakness were complications.

Diagnosis and management of this entity are briefly discussed.

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PHAGE TYPING OF ANTIBIOTIC-RESISTANT STAPHYLOCOCCI*

III. Infection, Crossinfection and Superinfection

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IN previous reports[1,2] the high incidence of similar phage patterns of the antibiotic-resistant staphylococci that were isolated from lesions from various clinical sources within a large medical center was noted. Over 48 per cent of the organisms that could be typed by present methods occurred in one of seven phage patterns (47/53/54/75, VA4/53, 7, 7/53, 53, 47/53/75 and 47/53/73), and over three fourths of those isolated from refractory staphylococcal lesions occurred in one of these phage patterns. Current studies indicate that approximately 70 per cent of the staff members of this installation carry antibiotic-resistant staphylococci with multiple resistance to penicillin, streptomycin, oxytetracycline, and chlortetracycline, whereas only about 6.7 per cent of blood-bank donors normally carry staphylococci resistant to penicillin alone.[3] Only 2 throat cultures from the latter group of 73 have thus far yielded organisms of multiple resistance.

Blair and Carr[4] presented evidence of the phage typing of a series of cases that they followed for varying periods up to eleven years. The relative constancy of the infectious agent in these cases was quite evident.

This report considers the problem in large medical establishments and gives further evidence of the origin of infection with pathogenic antibiotic-resistant staphylococci.

MATERIAL AND METHODS

The staphylococci were isolated from clinical material by routine clinical procedures. Organisms were maintained on trypticase soy-agar slants until used. Phage typing, with a complement of 34 staphylococcal bacteriophages, was accomplished by the methods adapted by Blair and Carr,[4] and interpretations conformed to data previously presented by us.[1,2]

RESULTS

Tables 1 and 2 describe the results of 23 cases of refractory staphylococcal infections observed in the last year. All but Cases 4, 6, 8, 11, 14 and 20 appear to have been initiated by crossinfection within the hospital with those antibiotic-resistant strains that are prevalent in this hospital. The cases listed above were native infections and in most cases appear to have been superimposed with a *"hospital strain"* on therapy during the hospital stay.

Three categories of infection, listed by number in the column headed "Remarks" in Table 1, were considered in the evaluation of the reported culture in each case: infection by crossinfection (1); after initiation of infection, persistence with the same or related strain (2); and superimposition of one strain on another (3a) and reinfection with different strains (3b).

DISCUSSION

The data presented illustrate that during the course of an infectious process the primary agent may be replaced by a seemingly unrelated strain of staphylococcus, whether or not the organism was initially resistant to the antibiotic. Among the cases in which the first staphylococcus isolated was sensitive to most antibiotics subsequent cultures demonstrated an antibiotic-resistant organism that by phage typing appeared to be unrelated to its predecessor.

In vitro studies with repeated exposure to various antibiotics have consistently failed to produce a change in phage typing. The problem of the origin of the resistant organism in the cases cited resolves itself as follows; either the organism was obtained by direct crossinfection with a hospital strain or it was present in the initial infecting flora in undetectable numbers—and on therapy was eventually selected and allowed to propagate. A recent report by Szybalski[5] elaborates this selection process for penicillin resistance. There is as yet no evidence of an organism that has maintained its original or related phage pattern and become resistant after or during therapy. The contribution of the human host to the alteration of the phage pattern of given strains of staphylococci is unknown. In view of the data of Blair and Carr[4] with repeated cultures over long periods alteration seems unlikely.

The patterns presented in Case 2 give striking evidence of replacement of an already antibiotic-resistant organism by one of specific resistance to erythromycin. During four months of a chronic chest lesion the etiologic agent appeared to be constant. Two months after erythromycin was started cultures resistant to the antibiotic were obtained—this organism did not appear to be related to the former by phage typing. This observation and other evidence presented in Cases 3, 4, 12, 14, 15 and 17 favor the phenomenon of crossinfection replacement rather than

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an actual development of resistance in vivo. However, there has been a report of a case of a coagulase-negative staphylococcus associated with a biliary-tract infection, which at the onset of therapy was initially sensitive to erythromycin. After three months of constant therapy the organism showed a significant increase in resistance but remained coagulase negative and could not be typed with the available phages.

TABLE 1. *Typing of Resistant Staphylococci.**

CASE NO.	CULTURE NO.	DATE	SOURCE	SENSITIVITY TO CHLORTETRACYCLINE	SENSITIVITY TO CHLORAMPHENICOL
1	A	2/13/53	Abscess of left hand	R	S
	B	2/25/53	Abscess of left hand	R	S
2	A	11/4/52	Chest empyema	R	S
	B	1/3/53	Chest empyema	R	S
	C	1/9/53	Chest empyema	R	S
	D	3/2/53	Chest empyema	R	S
	E	5/18/53	Chest empyema	R	S
3	A	3/23/53	Chest empyema	R	S
	B	4/9/53	Chest empyema	R	S
	C	4/20/53	Chest empyema	R	S
	D	4/22/52	Chest empyema	R	S
	E	4/28/53	Chest empyema	R	S
	F	6/6/53	Chest empyema	R	S
4	A	3/18/53	Drainage from ulna	R	S
	B	7/22/53	Drainage from ulna	R	S
5	A	4/15/53	Vagina	R	S
	B	4/24/53	Vagina	R	S
	C	5/1/53	Vagina	R	S
6	A	3/12/53	Throat	S	S
	B	4/21/53	Throat	S	S
	C	7/23/53	Throat	S	S
7	A	3/25/53	Right stump	R	S
	B	5/21/53	Right stump	R	S
8	A	4/21/53	Nose	S	S
	B	4/21/53	Urine	S	S
9	A	10/17/52	Conjunctiva	S	S
	B	4/18/53	Conjunctiva	R	S
10	A	3/11/53	Wound of face	R	S
	B	3/20/53	Wound of face	R	S
11	A	6/2/53	Drainage from right ear	S	S
	B	6/4/53	Drainage from right ear	S	S
	C	6/29/53	Drainage from right ear	S	S
12	A	3/3/53	Drainage from right ear	R	S
	B	3/9/53	Drainage from right ear	R	S
	C	3/15/53	Drainage from right ear	R	S
	D	5/9/53	Drainage from right ear	R	S
13	A	2/20/53	Inguinal abscess	R	S
	B	2/24/53	Inguinal abscess	R	S
	C	2/28/53	Inguinal abscess	R	S
14	A	6/15/53	Wound of right hip	S	S
	B	6/29/53	Wound of right hip	R	S
15	A	4/8/53	Wound of left leg	R	S
	B	5/29/53	Wound of left leg	R	S
16	A	2/20/53	Blood	R	S
	B	2/24/53	Cerebrospinal fluid	R	S
	C	3/13/53	Heart's blood post mortem	R	S
17	A	4/1/53	Drainage from left ear	S	S
	B	6/15/53	Drainage from left ear	R	S
18	A	3/16/53	Wound of left leg	R	S
	B	3/23/53	Wound of left leg	R	S
19	A	3/31/53	Wound of neck	R	S
	B	4/13/53	Wound of neck	R	S
20	A	3/12/53	Vulva	R	S
	B	5/18/53	Eye	R	S
	C	5/22/53	Vulva	R	S
21	A	1/26/53	Wound of left leg	R	S
	B	2/27/53	Wound of left leg	R	S
	C	3/25/53	Wound of left leg	R	S
	D	4/13/53	Wound of left leg	R	S
22	A	5/27/53	Throat	R	S
	B	6/16/53	Furuncle	R	S
23	A	11/4/52	Chest wound	R	S
	B	2/26/53	Chest wound	R	S
	C	3/19/53	Chest wound	R	S

*R = resistant; S = sensitive.

As indicated by Reiss et al.[6] there appears to be no correlation between antibiotic susceptibility and the

site of infection. Antibiotic-resistant organisms have been consistently isolated from deep-seated infections in this establishment, in contradistinction to the observations of Sheris and Florey.[7]

Summary

Evidence that infection with antibiotic-resistant staphylococci is primarily associated with a crossinfection replacement of flora phenomena is presented.

Table 2. *Further Typing of Resistant Staphylococci.**

Case No.	Sensitivity to Oxytetracycline	Sensitivity to Penicillin	Sensitivity to Streptomycin	Sensitivity to Erythromycin	Phage Pattern	Remarks
1	R	R	R	S	47/53/54/75	1,2
	R	R	R	S	47/53/75	
2	R	R	R	S	47/53/75	1,2
	R	R	R	S	47/54/75	
	R	R	R	S	47/54/75	
	R	R	R	S	47/54/75	—
	R	R	R	R	VA4/53	3a
3	R	R	R	R	6/47/53/54/75	1,2
	R	R	R	S	47/53/54/75	—
	R	R	R	S	53	3a
	R	R	R	S	No type	
	R	R	R	S	53	
	R	R	R	S	53	
4	R	R	R	S	42D	—
	R	R	R	S	7/53/54	1,3ab
5	R	R	R	S	53/76	1,2
	R	R	R	S	7/53	
	R	R	R	S	53/76	
6	S	S	S	S	3B/3C/39	
	S	S	S	S	42D	3a,b
	S	S	S	S	29/31/52A	
7	R	R	R	S	47/53/77	1,2
	R	R	R	S	47/53/55/77	
8	S	S	S	S	6/7	
	S	S	S	S	6/7/75	Related
9	S	S	S	S	52A	—
	R	R	R	S	54	3a,b
10	R	R	R	S	47/53/70/75	1,2
	R	R	R	S	47/53/75	
11	S	R	S	S	No type	
	S	R	S	S	42B	3a,b
	S	S	S	S	42B/47C/42C/31A	
12	R	R	R	S	47/53/75	1,2
	R	R	R	S	47/53/75	
	R	R	R	S	47/53/75	—
	R	S	S	S	VA4	3a
13	R	R	R	S	53	1
	R	R	R	S	47/53/54/75	—
	R	R	R	S	47/53	2,3ab
14	S	R	S	S	42B	—
	R	R	R	S	VA4/53	1,3a,b
15	R	R	R	S	3C/39/47/53	1,3a
	R	R	R	S	47/53/77	
16	R	R	R	S	54/73	
	R	R	R	S	47/54/73	1,2
	R	R	R	S	47/54/73	
17	S	S	S	S	6/47/53/54	—
	R	R	R	S	VA4	3ab
18	R	R	R	S	53	1,2
	R	R	R	S	53	
19	R	R	R	S	47/53/73	1,2
	R	R	R	S	47/54/73	
20	R	R	R	S	42B	
	R	R	R	S	42B	2
	R	R	R	S	42B/52	
21	R	R	R	S	47/53/73	
	R	R	R	S	47/54/73	1,2
	R	R	R	S	47/54/73	
	R	R	R	S	47/54/73	
22	R	R	R	S	53	
	R	R	R	S	53	1,2
23	R	R	R	S	54/73	
	R	R	R	S	47/54/73	1,2
	R	R	R	S	47/54/23	

*R = resistant; S = sensitive.

Observation of resistance to erythromycin in vivo in 1 case was accompanied by an apparent change in strain of the etiologic agent.

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SPECIAL ARTICLE

SYLVEST'S DISEASE (BORNHOLM DISEASE)

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THERE appears to be a remarkable degree of freemasonry amongst epidemiologists. I have visited many countries and have invariably experienced friendliness and cordiality from those of a like mind. An outstanding example of this was in July, 1936, as I was to include a two-day visit to Copenhagen in a Scandinavian cruise. When my friend, as he had become in the exchange of letters, Dr. Ejnar Sylvest, heard of this, he and his wife interrupted their annual holiday on Bornholm Island, opened up their house in Copenhagen and entertained my wife, daughter and myself in right royal fashion. It was an education to meet this serious-minded, intellectual general practitioner—just the sort of man, we all thought, we should ourselves like to have as our own family doctor — carrying his years lightly and striding through the town at a pace quite difficult for me to emulate. We wandered about the docks, where we saw the small packet in which he had come through the Baltic the previous day; we saw the fish market with its gleaming mounds of what looked the freshest of fresh fish and then settled down to a two-day tour of the town and systematic visits to hospitals and laboratories. Sylvest has done much with his life. I found then and have heard many times since of the soundness of his work as a general practitioner, but he has done more: among many excursions into epidemiology, he has, by his acute observations and great diligence, placed an unpleasant if nonfatal infectious disease in such a light that since his original monograph, it has been recognized in many countries and his description is so lucid that in *epidemics* — the isolated case is very different — a doctor must be very dull or very ignorant not to recognize it.

My first paper on the subject was entitled "Bornholm Disease," and for this I was severely scolded by eminent members of the profession in that I was instrumental in attaching the name of a beautiful island to a distressing malady and that another island, Malta, had suffered from a similar implication.

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But, although ever afterward I tried hard, by using the term "epidemic myalgia," to undo any harm I might have done, I am afraid the original name has prevailed and that is why I think it is high time it received the name under which this article is presented, Sylvest having done more than any man since the disease was first described to promote the knowledge of it. This will do away with such speculative names as *epidemic myalgia, epidemic pleurodynia* and *epidemic benign dry pleurisy,* for which there seems to be little justification.

I was privileged to discuss this article with the editor of the *Journal* last summer, and we agreed that the basis of it should be my own experience of the disorder, with references to the previous history and the recent exciting finding that the etiology was becoming clearer and that the Coxsackie viruses had been implicated as instrumental in it. That being so, I shall have to repeat my first experience, which has already appeared in these pages, since you, Sir, were kind enough to publish in 1948 the text of my Cutter Lecture of that year.

I must carry the reader back to the early morning of a bright July day in 1933, when I was roused from my bed by a young farmer, who I knew was of a placid disposition and gifted with common sense, but who on this occasion was thoroughly alarmed. "Would I come to see one of his small boys who had been taken seriously ill?" This boy had been quite well and lively, while being dressed, but was then attacked with a sudden pain in the upper abdomen, sweated profusely and was thought by his mother to have had a fit. When I saw him the pain was not so acute, but he was limp and deadly pale and looked extremely ill. He was taking short, sharp breaths, which were obviously causing him discomfort, but at this stage his temperature was only 98°F. Later in the morning my partner saw him in a return of the acute pain and suggested that the trouble was a painful cramp-like spasm of the respiratory muscles, probably the diaphragm. This was a very acute clinical observation that helped us materially in the final decision on the identity of the disease.

We saw the boy together at 3 p.m., and again the picture was changed. His face was flushed, his temperature was 101°F., and his respirations were definitely 60 to the minute. He was lying in a dazed condition, taking no notice of us while we examined him; his alae nasi were working, and he had an expiratory grunt and a short cough. At this point we felt ourselves on firmer ground and thought we were justified in suggesting that acute lobar pneumonia was beginning, although chest signs were completely negative. In the evening he was definitely improved, to add to our diagnostic difficulties if at the same time to bring us peace of mind. His temperature had fallen to 100°F., he had lost his respiratory distress and he had no pain. The next morning (really, we were dealing with a strange disorder) the little rascal, standing on the window-sill and thumping on the pane, greeted me smilingly but, I thought, derisively, as I walked up the garden path. I examined him carefully and could find nothing to account for the happenings of the previous day. I told his mother that I had not the slightest idea what had been the matter with him, but that he was now quite well and she should worry no more. This was a singularly unfortunate remark as the sequel proved, for on the following day the little fellow had a complete repetition of the first day of his illness with the addition of pains in the back, which prevented him from raising himself in the bed. The next day he had a "bad cold in the head" and his evening temperature was 99.8°F., but soon afterwards he recovered completely.

The family consisted of father and mother and 3 little brothers in addition to the first victim, and the boon companions of the boys were 3 little girls who lived on the opposite side of the main road. Two of these were bending over the little sufferer's couch, interest and solicitude depicted on their faces, on the very first day of the illness. I told the mother that these young women would be better off in their own home, until we had decided what was the matter with her own child, and packed them off, little thinking that the mischief had already been done. To shorten this somewhat lengthy story, 2 of the brothers sickened on the second and third days of the first boy's illness, and the 2 little girls on the fourth day. Four days after his boys' recovery the father became a victim.

We were therefore dealing with a small outbreak of a disease, obviously infectious, in which textbooks gave no help. We summarized the symptoms as follows:

Abrupt onset, with acute spasmodic pain in the upper abdomen, accompanied by profuse sweating.

Rapid, shallow breathing, obviously extremely painful, and pain on yawning and on deep breathing and laughing (between the spasms).

Temperature up to 103°F., rapidly subsiding, but tending to rise again about the third day and again on the fifth or sixth day.

Complete absence of vomiting; tongues coated, 3 of the white-strawberry variety.

No faucial injection, but nasal catarrh in 1 child and unilateral conjunctivitis, both probably incidental.

A trace of albumin in the urine of 1 child.

Pain in the knees in another.

No rashes.

Complete recovery in four to six days, with no sequelae.

There were now two problems for solution: where did this strange disease come from, and could we give it a name? The first was partially answered immediately. Four days before the first youngster fell ill, 2 children from the York neighborhood visited the farm to join in the fun of the haymaking. One of them, a girl, spent the day sobbing with pain doubled up on the sofa, and although I did not see her I have no doubt she was the source of the infection, but that is as far as it went and no further information was forthcoming.

The second problem was more difficult, but with the help of Sylvest I believe it was solved completely. We had both been interested in epidemics of jaundice and had had some correspondence on the subject. He naturally supplied me with reprints of this and other articles on a disease, which he called "myositis epidemica" or "Bornholm disease," asking if I had seen it and warning me to be on the lookout for it.

I completely forgot this until the present emergency, and then I could not read these Danish articles, but his references were to English and American papers on epidemic pleurisy, epidemic pleurodynia and, most of all suggestive, epidemic transient diaphragmatic spasm. I suspected at once that I was on the right track, and finally a copy of a paper in French on the subject submitted to the Office Internationale d'Hygiène Publique in Paris settled the matter without a reasonable doubt.

Sylvest's historical reviews are valuable, and they go back to 1856, when Jon Finsen observed this condition in Iceland but did not publish his findings until 1874, whereas in Norway it was described by Daae in 1872.

The latter's description of the symptoms, reproduced by Sylvest, is worth quoting:

> As a rule the patient has a stitch in one side of the chest, most often without any precursory ailment, but sometimes after an attack of chills; the stitch is often accompanied by pains in the back, shoulders, epigastrium and abdomen and these pains are described sometimes as oppressive, sometimes as shooting or aching; less frequently they are felt at the back of the head, neck, arms, legs and even in the fingers. There is considerable difficulty in moving the affected parts, especially the chest, therefore the respiration is laboured, sometimes to such an extent that the patient feels as if he were being strangled.
>
> Usually the general condition is much affected. There is as a rule some headache, pyrexia and thirst and the bowels are sluggish. The tongue is generally coated, the pulse normal or a little frequent. There is seldom any cough, so cough does not appear to go with this disease and physical examination of the chest reveals no abnormality.

In the United States Dabney, in 1888, was obviously writing of the same disorder in an account of an epidemic illness, resembling dengue, which had acquired the local name of the "Devil's grip." After a long interval it was again described in the United States and in 1924 in England. Three epidemics of what appears to have been the same condition were recorded, respectively, by Bruce Williamson, by Lloyd and by Attlee, Amsler and Beaumont as "Epidemic pleurisy." This disease was in many cases associated with a pleuritic rub, — not a physical sign in Sylvest's or my own patients, — but the symptoms were otherwise so similar that I believe it is safe to conclude that these writers were describing the same disease.

Later, in 1933, I had other sufferers quite unconnected with the small outbreak described above: 3 in 1934 and then, in 1936, 6 in one household in my own practice and 8 centered round a doctor's family in Northallerton.

This is a disease in which accurate diagnosis is most essential and in 1937, when I wrote an account in the *British Journal of Children's Diseases,* I listed the following three points that had helped me in diagnosis, besides the intermittent nature of the disease:

> The almost invariable absence of vomiting [two only of my first 31 patients vomited and none of the 48 seen since].
> The rarity and lack of prominence of cough [v.s. Daae].
> The greatly increased respiratory rate [whether the pain be thoracic or abdominal].

As far as my own further experience goes these points still hold. Records of other observers largely support me in these, but the absence of vomiting is not invariable. I have been privileged to read Dr. W. A. Brown's M.D. thesis before publication. His home is at Easington, County of Durham, where in 1951 he observed one of the largest epidemics yet recorded in England; this consisted of 115 sufferers, on all of whom careful records were kept. He has approached the subject from every angle and I shall anticipate with pleasure his article when it does appear.

In a personal communication, he tells me that vomiting was not a prominent feature, but in his thesis he relates that 23 of his 85 patients, fifteen years of age and under, actually did vomit.

The personal account given above is only part of my experience of the disease, since in 1949 we had 15 sufferers, who faithfully reproduced the picture of the former outbreaks. Previously, I had indulged in a cheap jibe at the expense of the surgeons that the only possible danger in the disease was that the sufferer might fall into their hands owing to a faulty diagnosis, and in the 1949 outbreak I crashed headlong into the trap myself. I have already said that the individual sufferer presents a different diagnostic problem from that of a sufferer in an epidemic.

The first of these mistakes was in a little girl three years of age, and of her I made the following note:

> Seen 12 p.m., lies doubled up on a sofa apparently asleep; suddenly cries out and is obviously in great pain; spasms recur and last from 3 to 5 minutes, the child relapsing into semi-consciousness in the intervals. No vomiting.

In the attacks she had an expiratory grunt and shallow, short inspirations, 30 to the minute, with no abnormality of the abdomen. She was sent to the hospital as probably suffering from acute intussusception, although with a caveat of Bornholm disease. However, the surgeon, and I believe he was justified, operated the same evening, only to find a perfectly normal abdomen.

The second patient, a woman of thirty-three, began with severe pain under the right costal margin on a Thursday. Again, there was no vomiting, but there was definite rigidity on that side of the abdomen. This remained constant on Friday and Saturday, and on Sunday, with pain and rigidity still persisting, she was sent to the hospital with a diagnosis of retrocecal appendicitis. If I had only felt justified in waiting one more day, 4 other members of the family developed *retrocecal appendixes,* which would have made the diagnosis clear and saved the poor woman an unnecessary operation. The absence of vomiting should have warned me in both these cases, and in the latter the fact that the initial pain was not generalized in the abdomen, but definitely in the right upper region. To my intense relief both patients made a complete recovery.

Many of these 15 patients showed the intermittent nature of the illness (not, unfortunately, the young woman described above), and an especial feature was pain at the root of the neck, connected no doubt with involvement of the diaphragm. The father of the boys in my first outbreak was the only one previously to show this symptom.

In this epidemic blood from 3 patients was sent to Dr. Marshall Findlay, and evidence of the presence of Coxsackie virus B was detected in each.

In 1951 we had an epidemic consisting of 31 sufferers, most of whom had the disease in a mild form. Two young children had symptoms akin to those of the child mentioned above who was unfortunately sent to the hospital, but the presence of the epidemic made the diagnosis clear.

It is not proposed to enter into the whole field of infections with the Coxsackie virus. In his William Henry Welch Lecture (1952) Professor Gilbert Dalldorf states that Bornholm disease is evidently a consequence of infection with the Group B Coxsackie virus. Group A strains have not been implicated; these seem to be connected with the syndrome of herpangina in children.

In this lecture he makes another most significant and interesting statement:

> The largest known epidemic of pleurodynia occurred in Sweden in 1931, when 12,000 cases are estimated to have occurred during the late summer. Professor Kling told me of that epidemic and has since supplied the Swedish poliomyelitis records. I was greatly interested to note that the number of cases of paralytic poliomyelitis

and of poliomyelitis deaths in 1931 were the least for the 20 year period covered by the records.

In this lecture he alludes to a previous paper, which gives proof that Group B Coxsackie virus prevents or delays paralysis in mice inoculated with the Lansing strain of poliomyelitis virus, in the same way as it has been known for years that experimental poliomyelitis is modified by intercurrent infection with the virus of lymphocytic choriomeningitis.

In this journal in 1952 Huebner et al., of Bethesda, Maryland, allude to the importance of the Coxsackie viruses, particularly in herpangina and epidemic pleurodynia.

Much other work has been done on this subject in the United States and also in England, notably by Findlay and Howard, and a new era appears to be dawning in the whole field of virus diseases, so widely spread does this group appear to be and because of the comparative ease with which it lends itself to handling in the laboratory.

It is beyond the scope of this article to review the whole literature of the subject, but epidemics in recent years have been reported as occurring in many different countries, in the United States, England (recently in Oxford, 1951, and Easington Colliery, 1951), Scotland, India, Aden, the Middle East, Holland and Australia, and the symptomatology in all these is clear cut and true to type. It is to be hoped that the disease will receive attention from the writers of textbooks, which its importance demands, so that no student will ever leave the hospital without the symptoms clearly fixed in his head.

For a relatively innocuous illness with no death rate it is remarkably successful as a mimic of serious disease both abdominal and thoracic, and unless the syndrome is very clearly defined many of these sufferers will find their way to the operating table as it is morally certain they have done in the past.

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MEDICAL PROGRESS

ANESTHESIOLOGY (Continued)*

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NEW YORK CITY

Dimethyl d-Tubocurarine

Dimethyl d-tubocurarine was synthesized by Collier et al.[71] in 1948 and introduced to clinical anesthesia in 1949.[72] Its action is similar to that of d-tubocurarine. Unna and his co-workers[73,74] compared its action with that of d-tubocurarine in man. Its duration of action is slightly shorter than that of d-tubocurarine. Its potency, as measured by depression of grip strength, is higher than that of d-tubocurarine (equipotent dose in micrograms of ions per kilogram was 107 for d-tubocurarine and 41 for dimethyl d-tubocurarine). According to their studies dimethyl d-tubocurarine has a higher coefficient of safety regarding the respiratory sparing effect as measured by the ratio of depression of vital capacity and grip strength (VC_{50}/GD_{95}: d-tubocurarine, 1.48 ± 0.48; dimethyl d-tubocurarine, 2.99 ± 1.19).

Flaxedil

Flaxedil, or gallamine (tri-[diethylaminoethoxy]-1,2,3-benzene), was first used in clinical anesthesia in 1949.[75,76] Its action at the neuromuscular junction is that of blocking of depolarization. In man, as shown by Unna et al.[77] its potency is one fourth that of d-tubocurarine (milligram for milligram). The peak paralyzing effect is reached in five or six minutes, and the duration of its action is shorter than that of d-tubocurarine. A cumulative action similar to that of d-tubocurarine was demonstrated both by these

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workers and by Marbury and his associates.[78] It does not block ganglionic transmission with skeletal-muscle paralyzing concentrations and does not liberate histamine, but it has a specific vagolytic action on the heart, resulting in tachycardia that lasts for twenty to thirty minutes. Because of this side action, Marbury et al.[78] warned against its use in patients with cardiovascular disorders.

Mytolon

Mytolon, WIN 2747 (2.5-bis-[3-diethylamino-propylamino] benzoquinone-bis-benzylchloride) was synthesized in 1948 by Cavallito, Soria and Hoppe.[79] It appears in red crystalline form, is readily soluble and stable at high temperatures, and is freely miscible with other intravenous agents. Hoppe[80] investigated its pharmacologic effect in laboratory animals and demonstrated that its action at the neuromuscular junction is similar to that of d-tubocurarine; in mice it is half as active and a fourth as toxic as d-tubocurarine. He also showed that Mytolon has an anticholinesterase activity about a fourth that of neostigmine, and that it produced a significant potentiation in the vasodepressor response after vagal stimulation and injection of acetylcholine, presumably owing to its anticholinesterase activity. It does not appear to have any significant effect on sympathetic ganglions. Arrowood[81] and Foldes, Hunt and Ceravolo,[82] reporting their clinical experience, observed that maximal relaxation occurred six to eight minutes after injection with an initial dose of 4.5 to 18 mg. The relaxation lasted seven to fifteen minutes, but recovery was gradual and not so sudden as that from decamethonium anesthesia. No bronchiolar spasm was encountered, but excessive salivation and bronchial secretion occurred quite frequently if premedication with belladonna drugs was not adequate. The "muscarinic" action on the salivary glands was also observed by Robertazzi,[83] but he noticed no excessive bronchial secretion. Robertazzi also observed that sinus bradycardia (rate of 60 per minute or less) occurred in 85 per cent of his cases. Foldes recommended adequate premedication with belladonna drugs (0.6 mg. of scopolamine) to prevent the excessive secretions and the vagotonic effects of Mytolon.

Decamethonium

Decamethonium, or Syncurine (bistrimethylammonium decane salts, C_{10}), was synthesized in 1948. Its relaxant action was reported by Barlow and Ing[84] and Paton and Zaimis[85] independently at the same time. Its action on the neuromuscular junction is that of depolarization of the motor end plate. In unanesthetized man Unna and his co-workers[73,74] observed that it is five times as potent as d-tubocurarine, weight for weight, and that in equipotent dose the respiratory paralyzing effect is more marked than that of other drugs studied (VC_{50}/GD_{95}: d-tubocurarine, 1.48 ± 0.48; decamethonium, 0.86 ± 0.07). The action of successive doses of decamethonium is not cumulative, and evidence of tachyphylaxis has been demonstrated. Its use in clinical anesthesia was reported by a number of authors.[86-89] The average initial dose is 1 to 4 mg. Its effects reached the maximum 4 to 6 minutes after injection, and the duration of action was shorter than that of d-tubocurarine, dimethyl d-tubocurarine, Mytolon and Flaxedil. Although the relaxation obtained with decamethonium was judged to be satisfactory in most cases, it was found that muscle relaxation can disappear suddenly, and sometimes the effect of repeated injections cannot be predicted because of tachyphylaxis. Furthermore, postanesthetic respiratory depression was common, and a number of patients had prolonged apnea after the administration of decamethonium. There was no evidence of histamine release or bronchiolar spasm and hypotension. Young[90] showed that decamethonium does not cross the placenta in concentrations fifty to a hundred times the paralyzing doses in rabbits and in guinea pigs.

Succinylcholine

The ability of succinylcholine to paralyze muscles was first demonstrated independently by Bovet[91] and Phillips[92] in 1949. It causes muscular relaxation by depolarization of the motor end plate, but the duration of action is exceedingly short. It is probable that succinylcholine is hydrolyzed by plasma pseudocholinesterase to succinylmonocholine and choline and then to succinic acid and choline[93] and that the hydrolysis is a zero order reaction at the rate of 0.03 to 0.06 micromols per cubic centimeter of plasma per minute.[94] Because the detoxification of succinylcholine depends on the activity of pseudocholinesterase its action can be greatly potentiated by anticholinesterases,[95] and in patients with low serum cholinesterase level, prolonged paralysis after succinylcholine was observed by Evans et al.[96] and Bourne, Collier and Somers.[97]

Thesleff[98] studied the action of succinylcholine comprehensively both in laboratory animals and in man. He observed that the dose and duration of paralysis had a direct relation. There was neither cumulative effect nor tachyphylaxis. Its action was potentiated by eserine, prostigmine, TEPP and Tensilon, whereas atropine had no effect. Transmission of impulses through the stellate ganglion and mesenteric ganglion was not changed until the concentration of succinylcholine reached six hundred and fifty to seven hundred times that of paralyzing concentrations. However, succinylcholine caused a slight depolarization of ganglionic neurons. This "nicotinic" action was thought to be responsible for the rise of arterial pressure that occurred when doses larger than 1 mg. per kilogram of body weight were injected. Exceedingly larger doses of succinylcholine (100 mg. per kilogram) caused a fall in arterial pressure, presumably from ganglionic blockade. The respiratory sparing action of succinylcholine was not noteworthy. Clinically,

bronchiolar spasm and excessive secretion of salivary and mucous glands were not observed. The problem of placental transmission was also studied by Thesleff in rabbits and in man. He found no evidence of fetal muscular paralysis after the injection of succinylcholine into the maternal circulation.

In clinical anesthesia succinylcholine is administered intravenously in the dose range of 40 to 60 mg. for short duration of relaxation. For sustained relaxation, it is given as a continuous infusion in 0.1 to 0.2 per cent solution. The degree of relaxation can be adjusted by regulation of the rate of infusion. It has proved satisfactory and relatively free from untoward side effects except for occasional hypertension. Cases of prolonged postanesthetic respiratory depression were reported and were generally thought to be the result of overdosage or low plasma pseudocholinesterase levels. Sometimes apnea persists even though muscular activity is restored. The mechanism of this phenomenon is not yet elucidated. Ellis et al.[99] found that some benzhydryl derivatives are quite active antagonists to succinylcholine, but no clinical trials of these compounds have been reported.

Myanesin

Myanesin, Tolserol (alpha-beta-dihydroxy-gamma-[2-methylphenoxy] propane) was used as a muscular relaxant, but it differs from the other relaxants in that its action is not on the neuromuscular junction but on the central nervous system. Berger and Bradley[100] demonstrated that it effectively antagonized strychnine convulsions, counteracted prenarcotic excitement and also increased the duration of barbiturate narcosis in nonparalytic doses. It possesses local anesthetic properties and in small doses depresses spinal-cord reflexes. The exact mechanism of action of Myanesin is not settled completely. However, evidence was presented that its action is mostly on the facilitatory and inhibitory systems of the central nervous system. Stephen and Chandy[101] showed that it does not alter cortical activity, and it has no effect on the muscular spasm of spinal-cord origin; they believe that the drug acts on the brain stem. Henneman et al.[102,103] and Kaada[104] concluded from their experiments that Myanesin decreases or abolishes the activity of the facilitatory and inhibitory systems and that neural circuits containing complex multisynaptic pathways are more vulnerable than direct two-neuron circuits. Myanesin is distributed widely in the body fluids and tissues[105] and is detoxified rapidly, probably in the liver, by conjugation.[106]

Clinically, earlier reports[107-109] showed that the administration of Myanesin as a 10 per cent solution was accompanied by a high incidence of thrombophlebitis from local irritation and by hemoglobinemia and hemoglobinuria. Berger[110] attributed these complications to the high blood concentration of the drug and suggested the use of a more dilute solution. Selvin,[111] employing a 1 per cent solution of Myanesin to evaluate its analgesic property in a group of 21 patients, encountered no complication of this nature.

Antagonists to Relaxants

It was mentioned above that "depolarization blocking" agents and depolarizing agents are mutually antagonistic; d-tubocurarine has an antagonistic action against decamethonium paralysis in laboratory animals,[112] and suitable doses of decamethonium also restore the neuromuscular transmission blocked by d-tubocurarine.[113] This pharmacologic phenomenon is, unfortunately, not useful clinically for the treatment of overdosage of certain relaxants.

In 1950 Randall[114] studied a series of phenolic quarternary ammonium derivatives for their anticurare actions. He found that one of these compounds, Tensilon (3-hydroxyphenyldimethylethylammonium bromide, Ro2-3198), has maximal anticurare activity with minimal toxicity. Further studies of the action of Tensilon were carried out by several groups of investigators. Hobbiger,[115] Nastuk[116] and Smith et al.[117] concluded from their experiments that the action is predominantly due to its anticholinesterase activity, although its effect is rapid and shorter than that of neostigmine. On the other hand Wescoe and Riker[118] demonstrated that Tensilon has a direct excitatory effect on unstimulated muscles similar to that of acetylcholine and neostigmine, and that curare and Tensilon are reciprocally antagonistic. They concluded that Tensilon antagonizes the curare action at the neuromuscular junction by its direct effect on the motor end plate and its competitive action against curare. At present the exact mode of action of Tensilon is not yet agreed on.

Artusio, Riker and Wescoe[118] studied the anticurare action of Tensilon in anesthetized man. With doses of 5 to 15 mg. given intravenously its action appeared within a minute and lasted from five to fifteen minutes. Transient bradycardia occurred in 77 per cent, and transient depression of arterial pressure in 10 per cent of their cases. Bronchiolar spasm and bronchorrhea were observed only occasionally in patients with a history of asthma. All the side actions were reversed by the administration of atropine. However, Foldes[119] stated that although no serious objections can be raised against the use of anticurare drugs, it is dangerous to use such agents without adequate supervision of the patients. Because of the relatively short duration of action the respiratory depression from curare can recur. He pointed out that it is safer to support the ventilation with oxygen until the return of adequate spontaneous respiration than to rely on anticurare drugs.

De Beer and his co-workers[120] have synthesized a number of drugs influencing neuromuscular transmission and found that a 2-stilbazoline derivative, Compound 49-204, antagonizes the action of decamethonium in mice, rabbits and dogs. They observed that small doses reversed the action of decamethonium block,

moderate doses caused weak ganglionic block and large doses produced marked curare-like action at the neuromuscular junction and respiratory depression. Vandam et al.[121] used this compound in man to antagonize the action of decamethonium. After doses of 50 mg. 17 of 35 subjects who were apneic with decamethonium responded within forty to sixty seconds with spontaneous respiration. There was also evidence of central stimulation: coughing, movement of the head and limbs and awakening. In the remainder of the patients studied 150 mg. was necessary to effect spontaneous breathing. Although the therapeutic range is wide, excessive dosage caused respiratory depression.

It is apparent that drugs differing in action can produce effective muscular relaxation for clinical surgery. Much remains to be learned about their mechanisms of action and the nature of their side effects. At present it can be stated with reasonable assurance that these compounds, properly selected and used judiciously in the maintenance of effective ventilation, are of considerable value in clinical anesthesiology.

Neural Basis of the Anesthetic State

The recent investigations of Magoun and his co-workers[122,123] on the physiology of the reticular activating system of the brain stem and the effects of various central depressants on its activity help in understanding of the state of wakefulness and that of anesthesia. These authors observed, in various mammals, that excitation of the central cephalic brain stem caused arousal of dormant animals, and destruction of this area produced a state of chronic unresponsiveness. They concluded that the brain-stem activating system seems to exert a desynchronizing influence on cortical and diencephalic structures during the state of wakefulness. During anesthesia with pentobarbital, ether and Dormison, French et al.[123] and Arduini and Arduini[124] found that the activity of this area was selectively depressed, whereas the activity in the lateral direct sensory pathways and primary sensory cortex was unaltered. Because the central anesthetics block synaptic transmission long before fiber conduction is affected[125] and transmission in the reticular activating system is mediated by multineuronal units, these findings indicate that depression of activity in this area and the cortical interneuronal system participated to a considerable degree in the production of the anesthetic state.

Clinical observations on the electroencephalogram during anesthesia made by Faulconer and his associates[126-128] appear to be consistent with this hypothesis. They classified the electroencephalographic patterns into six levels during thiopental, ether and cyclopropane anesthesia. The first level was characterized by breaking up of the resting rhythm into fast spike patterns of increased voltage. As consciousness was lost the fast frequency was admixed with slower frequency components of higher amplitude. Further deepening of anesthesia suppressed the voltage of these slow discharges as well as their frequency, and, finally, the electroencephalographic tracing became a flat line. The third, fourth and fifth levels corresponded to light, moderate and deep surgical anesthesia as judged by clinical signs. It is interesting that the slow, high-amplitude spike potentials during surgical anesthesia were strikingly similar to those recorded during natural sleep. If Magoun's[122] explanation of the anesthetic state is considered here, the selective depression of the brain-stem activating system during anesthesia would abolish its desynchronizing function, resulting in synchronized cortical discharge and loss of consciousness. Deeper anesthesia depresses the cortical activity and results in flattening of the waves of the electroencephalogram and loss of other neural activities.

The electroencephalographic patterns during anesthesia also have practical applications. Since the total energy output of the brain is related to the depth of anesthesia, the changes in frequency and amplitude of brain discharge may be utilized to regulate the rate of administration of anesthetics through a servo mechanism. Soltero et al.[129] administered surgical anesthesia in 50 cases with such a "servo anesthesia" device to maintain a constant level of anesthesia. They suggested that such a device is more desirable than the conventional method used to evaluate and maintain the depth of anesthesia for research purposes.

The blood concentrations of cyclopropane and ether at various levels of anesthesia were correlated with electroencephalographic patterns in surgical patients by Faulconer and his co-workers. During cyclopropane anesthesia the average blood concentrations were as follows: first level, 2.8 mg. per 100 cc.; second level, 5 mg. per 100 cc.; third level, 9 mg. per 100 cc.; fourth level, 13.8 mg. per 100 cc.; and fifth level, 16.5 mg. per 100 cc.[127] During ether anesthesia the respective concentrations were 52, 60, 84, 103 and 120 mg. per 100 cc., and 147-198 mg. per 100 cc. at the sixth level.[128]

These studies have advanced knowledge of the basic neural mechanisms of anesthesia to a degree that bears promise for significant progress in the future.

Spinal and Epidural Anesthesia

Helrich et al.[130] conducted quantitative studies on the fate of intrathecally administered procaine and the spinal-fluid levels required for surgical anesthesia in man. With repeated determinations after a single injection they showed that the decline of procaine concentration in spinal fluid is not due to chemical breakdown but to its absorption into the systemic circulation, where it is metabolized. They demonstrated further that the concentration at various levels of the subarachnoid space declines at the same rate and that the critical level for sensory anesthesia in the thoracic segments is 0.2 mg. per cubic centimeter. The problem of prolongation of spinal anesthesia with vasopressor

amines was also studied.[131] In the face of conflicting clinical reports on the efficacy of various vasopressor amines in the prolongation of anesthesia Helrich and his co-workers[131] found that 0.5 mg. of epinephrine prolonged procaine spinal anesthesia from 50 to 72 per cent; 2.0 mg. of Neo-synephrine prolonged the duration from 24 to 43 per cent, whereas 25 mg. of ephedrine had an erratic effect and did not predictably influence the duration of anesthesia. Clinically, the addition of vasopressor amines to anesthetic mixtures is open to question because of the possibility of ischemic damage to the neural structures.

Headache after lumbar puncture remains one of the most troublesome minor complications of spinal anesthesia. Its prevention and treatment have been the subject of many clinical reports.[132-137] The cause was discussed amply and found to be excessive loss of cerebrospinal fluid through the puncture site, disturbing cerebrospinal-fluid hydrodynamics. It was observed that headache is associated with a spinal-fluid pressure lower than normal. Furthermore, spinal fluid has been demonstrated in the epidural space in patients who have had a dural puncture.[134] Needles of small size (24 gauge or smaller) or with a pencil point have been used with a significantly reduced incidence of headache.[133,135,136] Adequate hydration of the patient to increase the production of cerebrospinal fluid was of value in both the prophylaxis and the treatment of this complication.[137] Other measures, such as epidural or subarachnoid injection of saline solution, were used for treatment, with some success.

Epidural anesthesia is of clinical value in that the possibility of headache and other complications can be avoided.[138] However, hypotension after an epidural block is just as frequent as that after a spinal anesthetic. The onset of anesthesia is usually slower, and the degree of anesthesia and muscular relaxation is not always as satisfactory as in subarachnoid block. These considerations will probably restrict the utility of this method as a substitute for spinal anesthesia.

The mechanisms of epidural anesthesia were studied by Rudin, Fremont-Smith and Beecher[139] in dogs and by Frumin et al.[140] in man. After deposition of procaine in the epidural space the presence of the drug in the spinal fluid in anesthetic concentrations was demonstrated. It was concluded that procaine diffuses through the dura and may block nerve conduction intrathecally. Frumin and his associates[141] suggested that the site of blockade with threshold concentrations of procaine is probably the dorsal-root ganglion.

(To be concluded)

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MEDICAL INTELLIGENCE

CARCINOMA OF THE RECTUM IN A CENTENARIAN

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THE following case presented a problem that, if not unique, was at least so unusual that the details of its management are worth recording:

H.R. (M.A.H. 111455), a 100-year-old woman, was admitted to the hospital on November 11, 1953 with a diagnosis of carcinoma of the rectum. She had been sickly as a child and recalled a number of childhood diseases, culminating in a severe attack of pneumonia; she had not been expected to survive to adult life. This prognosis had proved so inaccurate that she had outlived all her relatives, with the exception of a cousin, who was in comparatively good health at the age of 82 years, and a nephew, who was 65.

After her childhood she was comparatively immune to the current maladies. Protected by wise and generous parents she attained eminence as a musician, excelling both as a singer and as a pianist. Meanwhile, by devious methods, she achieved a physical durability that amounted almost to indestructibility. When she was queried concerning possible reasons to which her longevity could be ascribed, the only noteworthy feature appeared to be an antipathy to obesity and a distinct hatred of vegetables. In addition tobacco and alcohol had been religiously eschewed. She had remained a spinster.

At the age of ninety-seven she suffered from a 2d attack of bronchopneumonia. Recovery with the aid of penicillin was uneventful. From that time on she maintained a fairly comfortable existence. She was active in her apartment, restricted only by various bony and muscular pains arising from senile osteoporosis.

Shortly before her 100th birthday a new series of symptoms, consisting of rectal bleeding and constipation, developed. Two months later she was first examined by one of us (W.S.W.) because of these complaints, and a diagnosis of carcinoma of the rectum was made on digital examination. Immediate hospitalization and operation were advised but refused.

The Yankee constitution proving hardier even than expected, her vitality remained as the symptoms increased. Finally, however, about 8 months after the onset of the symptoms, her condition became so poor that she consented to hospitalization.

This consent was obtained despite her general objections to hospitals and doctors, which seemed perfectly reasonable since she had never been in the former and had practically never seen the latter. At the time of entry she was exceedingly costive, and, because of the frequent cramps of tenesmus, she attempted digitally to remove stools from the rectum. She was obviously in great pain with frequent movement of the bowels. In addition she had distressing urinary frequency and urgency, requiring evacuation of the bladder approximately every 30 minutes day and night.

Physical examination demonstrated a thin, wiry, well preserved woman, weighing approximately 90 pounds. The blood pressure was 120/80. The chest was clear. The abdomen was moderately distended; the liver edge was not palpable. Vaginal examination could not be carried out. Digital examination of the rectum showed a large carcinoma, beginning 4 cm. above the mucocutaneous margin and ex-

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tending above the reach of the finger. There were no enlarged lymph nodes. Peripheral circulation was normal. The digital findings were confirmed by sigmoidoscopic examination 2 days later, when a biopsy proved the diagnosis of carcinoma. The sigmoidoscope could not be passed beyond the growth, which almost completely blocked the lumen of the rectum 12 cm. above the sphincter. Barium-enema study thereafter revealed an extensive carcinoma of the rectum and rectosigmoid, with nearly complete obstruction. X-ray examination of the chest showed extensive osteoporosis, but there was no evidence of metastatic disease.

Some attempt to relieve her discomfort other than by the use of opiates was indicated, several alternatives being available. A simple colostomy would have relieved the obstruction. A combined abdominoperineal resection would have offered the best chance of cure, but at the price of a colostomy, which might have proved a great handicap at her age. A two-stage resection might have been safer. A perineal might have been more supportable than an abdominal colostomy. Radiation therapy could be considered. When all these alternatives were discussed, it was finally decided that the established principles of therapy should be followed and the best operation for cure selected. When the patient was apprised of this decision and the necessity for a colostomy, she met it with an equanimity that led us to believe that she failed to comprehend our explanation. It was not clear until several weeks later why the complications of a colostomy did not worry her.

Accordingly, after several days' preparation with enemas and Sulfathalidine, a Miles resection of the rectum was carried out on November 18. The operation was remarkable chiefly for its ease and for its toleration by the patient. She had a minimum of preoperative medication, and a low spinal anesthesia augmented by nitrous oxide, oxygen and ether. Her blood pressure was maintained at 120/80 to 100/70 during the 1 hour and 20 minutes required for the operation. The standard abdominoperineal excision was carried out, including removal of a huge megasigmoid packed with feces. An unusually wide perineal dissection was done. No gross evidence of metastatic disease was encountered. One transfusion of 500 cc. of whole blood was given.

Pathological examination of the resected specimen showed 48 cm. of rectum and sigmoid. The perineal skin measured 7 by 7.5 cm. The tumor began 4 cm. above the anus and was 5 by 8 cm. in size. A single lymph node was involved by metastatic disease, and microscopical examination of the local lesion showed adenocarcinoma extending through the bowel wall.

The postoperative course was entirely uneventful. The patient was ambulatory on the 2d day. She was put on a soft-solid diet on the 4th day, and the colostomy moved spontaneously on the 10th. The bladder catheter was finally removed 3 weeks after operation, and she voided normally thereafter. The abdominal wound was firmly healed, and the sutures were removed in 2 weeks. The gaping hole in the perineum granulated steadily and finally closed about 3 months after operation. The colostomy moved spontaneously once a day, and no enemas and no irrigation were required.

Physical rehabilitation thus was easily secured. The reconstitution of her *élan de vivre* was somewhat more difficult. For a few days after operation she greeted her doctors with pithy statements, saying "Get away, I want to die." Meanwhile, she berated the nurses, whom she accused of failing to cover her and thus threatening her with death from cold.

Later in her convalescence, when her doctor suggested to her that a very interesting commentary on the progress of medicine might be obtained if she would dictate her personal history to one of the nurses she agreed in unusual terms: "Yes," she said, "I have often wished I had an amanuensis."

Sometime later a Trask colostomy dome was brought in for her to wear. Throwing it to the other end of the room she observed that she might as well use a worn-out saucepan from her kitchen. Furthermore, she knew all she had to wear was a tiny piece of gauze over the colostomy. We wondered why she was so wise. She finally told us that her housekeeper had had a colostomy for 20 years, and that it was the easiest matter in the world to manage. Thus, one of the greatest preoperative worries was instantly dissolved.

At present the patient is nearing her 101st birthday. She leads a much more comfortable life than would have been possible if any other course had been followed.

Discussion

Stories of this patient's indomitable courage will support others in times of stress, for who should not get well if a woman of a hundred years can recover from such an operation? Her conduct has inspired her doctors, and it will sustain other patients. Aware of these effects she should find a reward even greater than relief from pain. Perhaps she can acquire the state of which Wordsworth wrote:

> An old age serene and bright,
> And lovely as a Lapland night,
> Shall lead thee to thy grave.

SURVEY OF SMOKING HABITS OF MASSACHUSETTS PHYSICIANS*

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In February, 1954, the Cancer Control Unit at the New England Deaconess Hospital Cancer Research Institute distributed a questionnaire to the members of the Massachusetts Medical Society. This report is based on 4104 completed returns received before April 1, 1954; the prompt response by so many members is indicative of their interest in the possible relation between bronchiogenic carcinoma and smoking.

A third (32.9 per cent) of the 4104 physicians report that they do not now use tobacco, although half of them (16.5 per cent) had previously smoked. A fifth (19.7 per cent) report that they are using less tobacco than five years ago; an additional 0.7 per cent have changed from cigarettes to pipe or cigar smoking, and 0.7 per cent state that they are considering whether to continue smoking. Three and three-tenths per cent volunteered the information that they are now using filtered cigarettes.

As a by-product of the questionnaire many helpful suggestions and useful supplemental remarks were offered. A few are included here for their general interest.

Heavy Smoking and Carcinoma

The question was asked whether, from the practitioner's personal outlook on the problem of smoking, he considered that "heavy smoking of cigarettes may lead to lung cancer." The word "may" was inserted in the statement since personal opinions were desired,

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not a reply to a proved or unproved statement. It is interesting that among the physicians who reported that they smoked *cigarettes* in appreciable quantities (more than an occasional cigarette) 55.5 per cent indicated their acceptance of the possible causal relation between cigarette smoking and lung cancer, whereas 62.9 per cent of those who reported that they did not smoke more than an occasional *cigarette* accepted the possible relation. This difference, although only 7.4 per cent, is significant when derived from a sample of 4100 (7.4±1.5). Unfortunately, there is no way to determine whether respondents do not smoke because they believe in the possible causal relation between cigarette smoking and lung cancer or whether persons who do not smoke cigarettes accept the possibility more readily. It is sufficient to observe that there is somewhat less cigarette smoking among physicians who state their acceptance of the possible relation (Table 1).

TABLE 1. *Response to the Statement, "Heavy Smoking of Cigarettes May Lead to Lung Cancer," according to Present Status of Cigarette Smoking.*

RESPONSE	CIGARETTE SMOKERS	NONSMOKERS OF CIGARETTES*	UNKNOWN SMOKING STATUS	TOTAL PHYSICIANS
	per 100	*per 100*	*per 100*	
Yes	55.5	62.9	†	59.2
No‡	35.2	27.6	0.0	31.4
Undecided	8.9	7.7	0.0	8.3
Unknown	0.4	1.8	†	1.1

*For this table "occasional" cigarette smoking has been classified as "nonsmokers of cigarettes."
†Numbers too small to indicate reliable proportions.
‡The questionnaire requested physicians to check statements that in their experience best indicated their personal outlook on the problem of smoking. Thus, statements not checked were assumed to be "No." A small number of questionnaires that were entirely blank except for the statement "Never Smoked" or "Nonsmoker" and so forth were coded as "Unknown Response" since it might be concluded that the physician did not disagree with the statements, but had not had time to give his opinion on them. However, if a portion of the questionnaire was completed even though none of the statements were checked it was decided that the record should be coded "No," assuming that the physician did not agree with the statement. It is believed that a number of these physicians did not disagree with the statements, but had not completed the questionnaire and that if they had done so more "Yes" and "Undecided" responses would have been obtained. There is no way to predict what proportion of these "No" responses actually represented an undecided or positive opinion.

TABLE 3. *Quantities and Types of Tobacco.*

QUANTITY	PERCENTAGE OF RESPONSE	PERCENTAGE OF SMOKERS
Cigarettes—per day:		
None	48.1	—
Under 1 package	19.6	37.7
One package	15.4	29.7
Over 1 package (not more than 2)	13.1	25.3
Over 2 packages	1.9	3.7
Occasional	1.7	3.2
Unknown	0.2	0.3
Cigars—per week:		
None	80.3	—
Under 15	8.8	44.7
15-28	3.3	16.6
29 and over	3.6	18.2
Occasional	3.7	18.8
Unknown	0.3	1.7
Pipe tobacco—per day:		
None	80.4	—
15 pipefuls or less	14.7	75.0
16-30 pipefuls	0.7	3.7
Over 30 pipefuls	0.2	1.0
Occasional	3.5	18.0
Unknown	0.4	2.2

PRESENT SMOKING STATUS

The present smoking status of the physicians is shown in Table 2, which is subdivided by age and sex. All other tables comprise the combined data. There were relatively few females in the study—the group of unspecified sex, owing to its distribution of smoking habits, must have been largely male. Although there was a progressive increase in the distribution of physicians who do not smoke as their age increases (29.5 per cent under forty, 32.3 per cent in the group forty

TABLE 2. *Present Smoking Status, by Age and Sex.*

SMOKING STATUS	AGE UNDER 40 YR.	AGE 40-59 YR.	AGE 60 YR. & OVER	UNKNOWN AGE	TOTALS
	NO. OF PHYSICIANS	NO. OF PHYSICIANS	NO. OF PHYSICIANS	NO. OF PHYSICIANS	
Males:					
None	277	599	252	13	1141
Cigarettes	379	656	165	15	1215
Other tobacco	104	259	157	8	528
Mixed*	178	335	115	5	633
Unknown	10	34	14	1	59
Totals	948	1883	703	42	3576
Females:					
None	17	48	27	7	99
Cigarettes	20	45	12	1	78
Other tobacco	–	1	–	–	1
Mixed*	–	1	–	–	1
Unknown	1	2	1	–	4
Totals	38	97	40	8	183
Sex unspecified:					
None	24	47	18	20	109
Cigarettes	38	65	14	4	121
Other tobacco	17	28	6	4	55
Mixed*	10	26	10	3	49
Unknown	3	5	–	3	11
Totals	92	171	48	34	345

*Combinations of cigarettes with cigars or pipe or both.

to fifty-nine and 37.5 per cent in the group sixty and over) the age factor was not considered of sufficient importance to warrant making the remaining tables more complicated by additional subdivisions.

TABLE 4. *Present and Past Smoking History.*

SMOKING STATUS	PRESENT SMOKING STATUS %	PAST SMOKING HISTORY %
None	32.9	16.4
Cigarettes	34.5	43.5
Other tobacco	14.2	13.9
Mixed*	16.6	22.8
Unknown	1.8	3.5

*Combinations of cigarettes with cigars or pipe or both.

Quantity of Cigarettes

Table 3 presents the quantity of tobacco, in different forms, used by the physicians in Massachusetts. At present 48.1 per cent of the physicians are not smoking any cigarettes; an additional 1.7 per cent smoke cigarettes only occasionally. Only 1.9 per cent report smoking more than 2 packages of cigarettes per day.

Quantity of Cigars

The percentage of the physicians who reported smoking no cigars was 80.3, and an additional 3.7 per cent smoked cigars only occasionally, in contrast to the 3.6 per cent who smoked 29 or more cigars a week. It is interesting that in this sample there was apparently a higher percentage of heavy cigar smokers than heavy cigarette smokers, despite the fact that a smaller percentage of physicians smoke cigars than cigarettes. (Sadowsky, Gilliam and Cornfield* have compared, "by weight," 1 cigar to 10 cigarettes; thus, 28 cigars a week, or an average of 4 cigars a day, have been considered equivalent to 40 cigarettes, and the classification of 29 cigars a week and over may be assumed to be "heavy" cigar smoking—equivalent to smoking over 2 packages of cigarettes a day.)

TABLE 5. *Replies to the Question, "Have You Changed Your Smoking Habits as a Result of Recent Lung-Cancer Publicity?"*

RESPONSE	PERCENTAGE OF TOTAL REPLIES
No	63.5
Yes	15.1
No, but changed for other reasons	3.0
Never smoked*	16.4
No, but intend to stop	0.4
No, but considering stopping	0.3
Unknown	1.3

*Includes physicians who tried smoking for a short period only — generally during childhood.

Pipe Smoking

Pipe smoking has been classified as none, occasional, 15 pipefuls or less a day, 16 through 30 and over 30; 80.4 per cent of the physicians reported no pipe smoking, and 3.5 per cent smoked only occasionally. Smoking of more than 30 pipefuls a day was reported by 0.2 per cent.

*Sadowsky, D. A., Gilliam, A. G., and Cornfield, J. Statistical association between smoking and carcinoma of lung. *J. Nat. Cancer Inst.* **13**:1237-1258, 1953.

DISCUSSION

Table 4 shows the present smoking status for the entire group and includes the past smoking history, which is not as reliable as the present smoking status, for some physicians did not furnish complete replies on past habits. Table 5 presents the distribution of replies to the question, "Have you changed your smoking habits as a result of recent lung-cancer publicity?" Table 6 indicates the quantity of smoking at present as compared with five years ago; whenever no change in smoking habit was indicated by the respondent it was assumed that the present *amount* of smoking was the same as that of five years ago. This may not have been an entirely justifiable assumption, and thus the figure of 60.0 per cent of physicians who appear to be smoking the same amount may be too high. It should further be noted that this 60 per cent includes physicians who had previously smoked but who had stopped before the last five-year period, since this group is smoking the same amount (no tobacco) now as previously. An additional 16.4 per cent indicated that they had never smoked more than a few months (childhood sampling), if at all. For purposes of simplification this group is labeled "Never Smoked."

TABLE 6. *Quantity of Smoking Compared with Five Years Previously.*

REPORTED COMPARISON	PERCENTAGE OF TOTAL RESPONSE
More	0.7
Same	60.0
Less	19.7
Never Smoked*	16.4
Changed to pipe or cigars	0.7
Unknown	2.5

*Includes physicians who tried smoking for a short period only — generally during childhood.

Fifteen per cent of the physicians stated that they had changed their smoking habits because of the recent publicity on lung cancer (Table 5), whereas only 3.0 per cent indicated a change in smoking habits for other reasons. It is likely, as specifically mentioned by some respondents, that many of the 744 who reported a change for one reason or another actually changed their habits for a combination of reasons and that the cancer publicity was the "last straw." Irrespective of whether a single reason or multiple reasons were responsible, the salient fact is that *a large number of Massachusetts physicians have changed their smoking habits.* Furthermore, a number of physicians state that they have already smoked for many years and thus believe that to stop smoking would have little effect on their health. This may, as suggested by at least one respondent, partially explain the discrepancy between the belief that smoking cigarettes may be related to lung cancer and the continuation of cigarette smoking; it is probable that this group includes those who are

firmly convinced that carcinogenesis is irreversible.

One physician states that in his experience "patients are now requesting guidance on whether to stop smoking as a prophylaxis against lung cancer." This is indeed a serious problem and one that is far beyond the scope of this survey.

Under "remarks" some have asked for suggestions on how to proceed to stop smoking. Again, this is beyond the scope of the survey. A number of methods mentioned by other physicians from their personal experience with stopping the smoking habit included gum chewing, candy eating, switching to smoking tea leaves or dried sweet fern and other herbs, which discourage the desire to smoke. Any innocuous device that will bridge the gap and serve to relieve associated tension tends to help break a deep-seated habit. As stated above, whether such methods should be encouraged is beyond the scope of this study.

Many interesting suggestions were offered in the individual responses to the questionnaire—for example, the possibility that "coughing is a form of irritation and its effect on cellular metabolism may be neoplastic over a period of time." Others included the apparent relation between tobacco and peptic ulcers and the possibility of a study of tumors of the gastrointestinal tract in relation to smoking habits since it was believed by some respondents that "it is more difficult to correct inflammatory conditions of the stomach, duodenum and large intestines in a smoker if he persists in smoking than if he stops."

Another answer suggested "the possibility that cigarette smoking provides a trigger mechanism that may have something to do with the origin of lung cancer in susceptible hosts." Several emphasized the importance of other variables, such as inhaling (deeply, shallowly, or not at all), rapid vs. slow smoking, the use of filters, the question of kinds and types of persons (those who become allergic to tobacco as opposed to those who apparently do not), duration of smoking, chemicals introduced into cigarettes and not in other types of tobacco, cigarette papers, the poisonous effect of nicotine and tars and the general abuse of drugs that are poisonous when improperly taken; all deserve careful consideration in studies of the problem of lung cancer.

Conclusion

A suggestion offered by a physician from Lynn is noteworthy:

> I believe the tobacco industry should divert 50 per cent of its advertising budget to impartial scientific research on this question and, if tobacco is found to be criminally involved, continue research for processes that will eliminate the danger. If, on the other hand, tobacco is found not guilty, the money spent will be the greatest single investment ever made on a selling point to the public, with far more appeal than any previous slogans or inferential pseudoscientific statements.
>
> Finally, if tobacco is found guilty and no methods can be devised to render it innocuous it should be outlawed as other noxious or dangerous substances are, or at the very least subjected to national referendum concerning processing, distribution and advertising.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40241

Presentation of Case

A three-week-old male infant was admitted to the hospital because of diarrhea and vomiting.

The child had been delivered spontaneously at another hospital and weighed 6 pounds, 4 ounces, at birth. A few attempts were made to nurse him but he vomited and therefore was given a formula of whole milk, water and Karo. At discharge from the other hospital on the sixth day he had lost 9 ounces. The mother was assured that he was a normal child. After being taken home he seemed always hungry but "spit up" about 1 ounce of every 3-ounce feeding. After each feeding he had a green, solid stool. The family doctor changed the formula to 15 ounces of whole milk, 5 ounces of water and 3 tablespoons of Dextri-Maltose. For the last ten days, on this formula, he "seemed better," but there had been no apparent weight gain and he continued to "spit up" about a third of the feeding. The stools, which were yellow and formed, numbered about six daily. He had always been willing to eat again immediately after "spitting up" a feeding. For the last three days he had coughed and sneezed frequently. Early in the morning of the day of admission he awoke crying, vomited three or four times and had several yellow, loose stools in rapid succession. Since that time he had been fretful and wakeful, and approximately six more loose stools were passed intermittently during the day. Occasional vomiting continued, and he was brought to the hospital in the evening.

The mother, who was twenty-seven years old, had suffered from a severe cough throughout pregnancy, and during the recent post-partum period had been treated for an "infection in her womb," but had left the hospital on the sixth day against advice. The father was thirty-nine years old and in good health. The family all slept in one room of an extremely cold

and damp three-room apartment. A sister twenty-two months old was in good health but had had diarrhea two weeks previously.

Physical examination showed a thin, lively infant with a lusty cry who appeared chronically malnourished but had fairly good skin turgor. Except for a moderately tense and protuberant abdomen the examination was negative. He weighed 6 pounds, 7 ounces, was 48 cm. long and had a head circumference of 35.5 cm.

The temperature was 98.6°F. by rectum, the pulse 150, and the respirations 24.

The urine was clear and pale yellow, had a specific gravity of 1.010 and was otherwise normal. Examination of the blood revealed a hemoglobin of 16 gm. per 100 cc., a hematocrit of 41 mm., a sedimentation rate of 4 mm. per hour, and a white-cell count of 17,200, with 52 per cent neutrophils, 43 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophils. The nonprotein nitrogen was 13 mg., and the total protein 3.4 gm. per 100 cc.; the sodium was 134 milliequiv., the chloride 107 milliequiv., and the potassium 5.3 milliequiv. per liter. A stool was negative for enteric pathogens, ova and parasites. Agglutination tests for typhoid and brucella organisms were negative. In stool trypsin studies x-ray film strips were digested by the stool in dilutions of 1:128. Roentgenograms of the chest demonstrated clear lungs and a normal-sized heart. A plain film of the abdomen did not show any enlargement of the liver and spleen. The gas pattern of the bowel was normal. No abnormal calcification or congenital anomalies were visualized.

Oral feeding was attempted initially, but because of persistent vomiting parenteral administration of fluids was substituted. The stools were frequent, yellow and soft. On the fifth hospital day moderate generalized edema developed and persisted; 5 gm. of salt-poor albumin was given intravenously, and the patient was started on oral skimmed-milk. When oral feedings were started, vomiting recurred, and pasty, green-yellow stools became frequent, so oral feeding was again stopped. A stool specimen was guaiac negative.

Roentgenograms of the chest eleven days after admission disclosed an area of consolidation in the axillary portion and posterior segment of the right upper lobe. The right lower lobe and the left lung appeared somewhat emphysematous. On the fifteenth day coughing and an increased respiratory rate became evident. He was vomiting and seemed occasionally to aspirate the vomitus. He was becoming anorexic, lethargic and pale, whereas previously he had been very active and hungry. The liver edge was felt 4 fingerbreadths below the right costal margin; pedal edema persisted. There was no fever. Leukocytosis (counts ranging from 15,000 to 25,000) persisted; the differential was essentially as before. He was given penicillin, streptomycin and chloramphenicol. A paracentesis of the right tympanum was performed, and a few drops of purulent material obtained. Culture of this grew out moderate pneumococci, and a few colonies of *Staphylococcus aureus*. On the same day he had a generalized clonic convulsion, which several minutes later became right sided and ceased after 30 mg. of Dilantin and 1 cc. of 10 per cent calcium gluconate had been given intravenously. A lumbar puncture done at this time revealed no increase in pressure. The spinal fluid was clear, contained no cells and demonstrated no growth when cultured. The next day respirations became labored, and his color was ashen. An x-ray film of the chest showed atelectasis of the right upper lobe, a low left leaf of the diaphragm and herniation of the left lung into the right hemithorax. A nasopharyngeal culture was reported as disclosing abundant growth of *Staph. aureus* and moderate growth of pneumococci, *Escherichia coli, Staph. albus* and diphtheroids. Respiratory difficulty increased, with episodes of tugging respiratory movements. On the twentieth hospital day an x-ray film of the chest revealed a new area of consolidation in the left upper lobe; the consolidation in the right upper lobe was unchanged (Fig. 1). On the twenty-third day there were two episodes of hematemesis, in which small amounts of guaiac-positive coffee-grounds material were expectorated. The stools were not tarry and grossly did not appear to contain blood. A film of the chest taken on the twenty-third hospital day showed almost complete consolidation of the right lung, with persistence of the consolidated area in the left-upper-lung field (Fig. 2). Respiratory distress increased, occasional hematemesis continued, breathing became irregular, and he died on the twenty-fifth hospital day. A barium-swallow examination on the day of death demonstrated a normal esophagus. Earlier on the same day a small, dark blood clot was found on the diaper.

Differential Diagnosis

Dr. Ralph A. Ross*: "A few attempts were made to nurse him, but he vomited and therefore was given a formula . . . ." That is a sad commentary on the lack of enthusiasm that many people have for breast feeding.

I shall start in the reverse order by discussing the later symptoms first. The evidence of slight bleeding from the gastrointestinal tract suggests agonal ulceration, a Curling ulcer or an esophagitis due to frequent regurgitation. I gather that was the reason for the barium-swallow examination within twenty-four hours of death. The respiratory symptoms certainly were the prominent ones at the end. The x-ray findings should help me; may we see the films?

Dr. C. C. Wang: The films of the chest taken on admission reveal essentially clear lungs; the cardiac shadow is not unusual. Approximately a week after admission the film of the chest shows an area of consolidation in the right upper lobe, which is also some-

*Physician, Children's Medical Service, Massachusetts General Hospital.

what reduced in size. In subsequent examinations the lesion in the right upper lobe remains unchanged, and there are new areas of consolidation in the left lower lobe. Four days later there is a new area of increased density in the left upper lobe, but the consolidation in the left lower lobe has disappeared (Fig. 1). In films taken just before the patient's death the right lung is completely opaque, and the consolidated process in the left upper lobe remains (Fig. 2).

DR. ROSS: Did you say pneumonia in distinction from collapse?

DR. WANG: I think there are both pneumonia and collapse. The remaining lung tissue is more expanded than normally.

DR. ROSS: There is striking evidence of lung changes. Was that primarily due to infection or to obstruction? It seems from the changing pattern and the rapid progression that this was much more likely on the basis initially of obstruction with infection playing a secondary role. That is pointed up by the

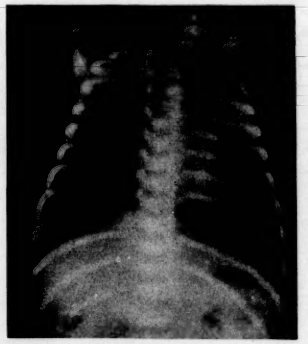

FIGURE 1.

persistent elevation of the white-cell count and the findings by the bacteriologist. The convulsive seizure was possibly due to anoxia or hypoxia resulting from the interference with the respiratory exchange. It would be interesting to know what the chemical determinations on the cerebrospinal fluid showed. There is no note about whether the protein was elevated in the cerebrospinal fluid.

DR. ALLAN M. BUTLER: It was not elevated; the spinal fluid was clear.

DR. ROSS: The convulsion could have been due to thrombosis or an embolic phenomenon on the basis of generalized infection. The sudden enlargement of the liver suggests that there may have been some right-sided heart failure, presumably on the basis of the lung changes.

To start back at the beginning from birth to the age of five weeks the child's behavior was considered to be within normal limits. The moderate regurgitation of formula certainly is not rare in infants who subsequently turn out to be perfectly normal. The caloric intake was quite low, and the formula, even if all of it was retained, just met the infant's requirements so that we have a suggestion that he was on a markedly reduced intake. He gained appreciable weight, however, for at the age of a week he weighed 5 pounds, 11 ounces, and on admission to the hospital he weighed 6 pounds, 7 ounces. Then he had an

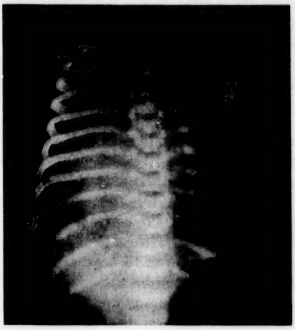

FIGURE 2.

acute gastrointestinal upset, perhaps related to the similar disease in the sibling in the household. At the time of hospitalization it apparently was agreed that this child was not seriously sick. There was some evidence of dehydration, as indicated by the hematocrit and the chemical determinations. The low serum protein fits in with the poor caloric intake—an aggravation of a normal physiologic drop in serum protein during the neonatal period—and, one would guess, was the cause of the appearance of edema when fluid was administered parenterally.

What factors connect these two periods? There was mild respiratory disease before admission, and the appearance of x-ray signs before he actually had symptoms of respiratory distress. In the family history the mother's cough throughout the nine months of pregnancy suggests that there may have been some relation. Could this have been due to acute tuberculous infection in the infant? One would have to suppose that he was infected in utero and, therefore, that the mother had tuberculosis of the placenta. All I can do is speculate; I have no evidence to carry that farther. Did a low-grade septicemia develop in the newborn period owing to sepsis in utero? Were blood cultures taken during hospitalization? The absence of fever in an infant does not rule out the possibility of sepsis; however, the vigor of the infant at the time of admission is against a sepsis of this duration.

Congenital malformation, obstruction to the esophagus or trachea, or both, meconium ileus and vascular rings might be considered. There is no evidence to support them. In summary we are presented with a malnourished infant with a distended abdomen, re-

spiratory changes of atelectasis and emphysema, infection of the upper respiratory tract with *Staph. aureus* predominating and hepatomegaly that could have been due to inspissation of biliary secretions or possibly to right-sided heart failure. All these findings can be explained by the disease that in Boston we call mucoviscidosis, the major finding being pancreatic fibrosis. But there was high tryptic activity in the stool. This test is not specific; if it had been negative, I should feel happier about this diagnosis. The finding of fairly good tryptic activity does not help me too much. In the early weeks, particularly, decreased duodenal tryptic activity is not present. Even in some of the later and proved cases of mucoviscidosis the trypsin has been within normal limits. The absence of change in the stool quality, I think, is explained on the simple milk intake. I shall end up, therefore, with the diagnosis of mucoviscidosis.

DR. JOHN B. STANBURY: Do you ever see this from nutritional factors alone?

DR. ROSS: Yes; but I think a five-week period is too short for this condition to have developed.

DR. BUTLER: Dr. Stanbury raised the question that was raised when this case was presented at a Tuesday general rounds. I believed that malnutrition was a major factor in the course of this infant's illness. Here was an infant who had had difficulty ingesting food ever since birth and had been both vomiting and having diarrhea off and on. On admission chronic malnutrition rather than dehydration was noted as the most striking finding. The parenteral fluid therapy that was indicated, therefore, was to meet severe nutritional deficiencies as well as to establish rehydration. This child had not had adequate vitamins, had not had adequate protein and had not had adequate calories. Hence, the administration of amino acids, ascorbic acid and components of the vitamin B complex, in addition to glucose and multiple electrolytes, was essential. Even in the absence of calories adequate to cover caloric needs amino acids should improve nitrogen balance and well-being, particularly of a severely depleted person whose homeostatic functions are geared to conservation and anabolism. This has been shown by Cox, Ellington and Mueller[1] in experiments on depleted rats. Also, in spite of the hemoglobin levels, transfusions appear to have been indicated in the case under discussion. Dr. Ross has mentioned infection; I assume that the child had infection. He may also have had mucoviscidosis. But I am particularly anxious to hear what importance the pathologists ascribe to the malnutrition of this patient.

DR. GERTRUD C. REYERSBACH: Do you think the child could have had one of the minor tracheo-esophageal fistulas that cause so much trouble in the lungs?

DR. ROSS: Yes; I think that possibility certainly has to be considered, but we have nothing further to go on.

DR. STANLEY BERLOW: On admission, this patient was thought to have acute diarrhea superimposed on chronic malnutrition. When the diarrhea abated after prolonged intravenous therapy severe respiratory distress developed, and he remained in an "Isolette" for the latter half of his hospital stay. We believed that the pulmonary disease was a staphylococcal pneumonia and treated him accordingly. On several occasions the radiologists did raise the possibility of aspiration. We thought this unlikely since he was fed almost exclusively by fluids intravenously.

CLINICAL DIAGNOSIS

?Pancreatic fibrosis.
Pneumonia.

DR. RALPH A. ROSS'S DIAGNOSIS

Mucoviscidosis.

ANATOMICAL DIAGNOSES

Malnutrition, neonatal, with changes in pancreas and liver.
Bleeding duodenal ulcer, with massive hemorrhage into gastrointestinal tract and lungs.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: At autopsy this child was marasmic, apparently severely undernourished. Since one of the diagnoses ante mortem was the same as that made by Dr. Ross we examined the pancreas quite carefully in the gross; it was perfectly normal in size, weight and appearance. The microscopical sec-

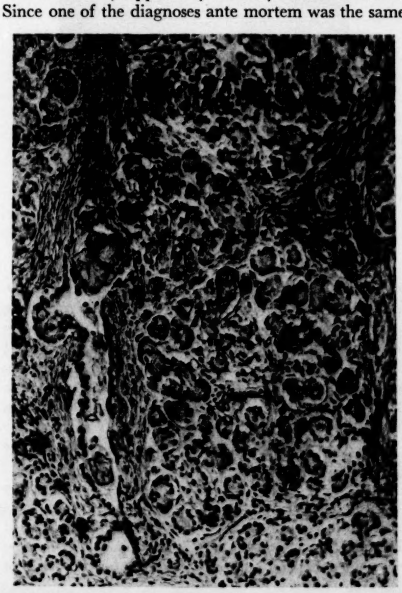

FIGURE 3.

tions, however, were definitely abnormal. The pancreas of a normal child of the same age as the child under discussion has closely packed acini and ducts. The pancreas of this child did not have this density. There was an increase in the stroma; some of the acini were markedly distended and there was definite inspissation of secretion in the ducts (Fig. 3). From the microscopical appearance we thought that this was consistent with the early stage of pancreatic fibrosis or mucoviscidosis, not unlike one of the photomicrographs in Farber's[2] first article on this subject in 1944, in which he described an early case. On the other hand similar changes have been described in severe malnutrition by the Gillmans[3] in South Africa and by others[4] from countries where malnutrition in children is common.

DR. STANBURY: What does the pancreas show in kwashiorkor?

DR. CASTLEMAN: I believe similar changes are seen. Although it is possible that the case under discussion was an early case of pancreatic fibrosis I believe that malnutrition was probably the major factor and that the pancreatic changes are consistent with the malnutrition.

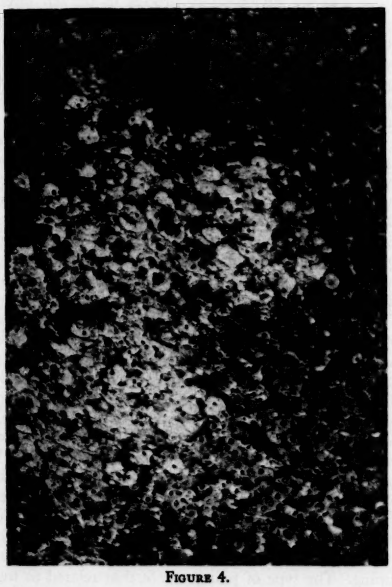

FIGURE 4.

In the liver there were many areas that at first glance appeared to be focal areas of fatty vacuolization, but the fat stains were negative, as were glycogen stains (Fig. 4). These changes are similar to those described in experimental anoxia and malnutrition by the Gillmans.[5] Further evidence that this was a case of acute malnutrition can be seen when one examines the thymus gland. A normal thymus gland in a child of this age should have a well developed cortex and medulla. This child had a very small and markedly involuted thymus gland—a finding very characteristic of malnutrition. There was practically no cortex left.

The immediate cause of death was related to the hematemesis. The first portion of the duodenum contained a deep, acute ulcer, in the center of which was a vessel that was actively bleeding. Microscopically, the ulcer had the fibrinoid base characteristic of peptic ulceration. The ulcer had penetrated almost through the muscularis and seemed ready to perforate. I believe this ulcer was a manifestation of the malnutrition. There was complete collapse of the right upper lobe caused by a mucous plug in its bronchus. All the bronchi and alveoli of the other lobes were filled with blood apparently aspirated from the hematemesis.

DR. HELEN S. PITTMAN: Was the brain examined?

DR. CASTLEMAN: The brain was normal.

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CASE 40242

PRESENTATION OF CASE

A twenty-seven-year-old nulliparous housewife entered the hospital complaining of diarrhea.

About a year previously the patient had noticed the gradual onset of weakness and malaise, with intermittent, moderately severe, aching pain in the lower abdomen most marked in the left lower quadrant. Two or three times in the course of the year, the pain became more severe, and was associated with diarrhea. The last such attack was four months before admission here, when she was admitted to another hospital. At the time she thought she had a fever, and believed she received intravenous infusions of fluids and penicillin or sulfadiazine. She left the other hospital against advice. Two or three weeks before admission ill defined pain in the left lower quadrant returned, and persisted to the time of admission. Three days before admission diarrhea began, with about a dozen loose stools in the course of the day. The character of the stools was not well described, but they apparently did not contain blood or mucus. Two days before admission, she awoke to find that she had passed a stool in bed. Diarrhea continued, now with vomiting. She thought she was febrile. On the day of admis-

sion she felt better and went shopping, but fainted and was brought to the hospital.

The menstrual periods had usually occurred every twenty-eight days and had lasted for five days. Six months before admission a period had been missed; thereafter they were more scanty, lasting only two days. There had been none in the last two or three months. The patient did not know whether or not she was pregnant.

Nine years before admission she had been jaundiced, and was kept in bed for six weeks. She was told that she had "bladder disease." She was married at twenty, but divorced a year later. One year before admission, she remarried. She was described as of low intelligence. In childhood she had lived in Florida, and only reached the eighth grade at school.

Physical examination showed a somewhat dehydrated woman who appeared acutely ill and complained of abdominal cramps. The heart was not enlarged, but there was a Grade 1 apical systolic murmur. The abdomen was slightly tender, and the muscles were held tense, especially in the left lower quadrant. An ill defined mass could be felt in the left lower quadrant, and this mass was acutely tender. Peristalsis was active. Pelvic examination disclosed a scarred cervix, but no softening of the isthmus. Muscle spasm prevented palpation of the fundus. The left fornix was tender, and bimanual examination demonstrated the tender mass in the left lower quadrant to be about 6 cm. in diameter. Rectal examination also revealed tenderness on the left. A stool was liquid but guaiac negative.

The temperature was 98.4°F., the pulse 80, and the respirations 23. The blood pressure was 110 systolic, 92 diastolic.

The urine was amber, had a pH of 6.0 and a specific gravity of 1.025, and contained no albumin, sugar or bile. Examination of the blood revealed a hemoglobin of 14 gm. per 100 cc. and a white-cell count of 27,400, with 84 per cent neutrophils. The serum sodium was 133 milliequiv., the potassium 3.7 milliequiv., the chloride 99 milliequiv., and the carbon dioxide 27 milliequiv. per liter, and the nonprotein nitrogen was 20 mg. per 100 cc. A stool culture grew out no pathogenic organisms.

At proctoscopic study the instrument was passed for 10 cm., but spasm prevented further examination. The mucosa was reddened and bled easily. Small shreds of yellowish mucus were seen, but no ulcers.

An operation was performed on the day of admission.

Differential Diagnosis

Dr. Gordon A. Donaldson*: I am going to have to ask the radiologist for some help.

Dr. Joseph Hanelin: No x-ray films were taken.

Dr. Donaldson: I am surprised that a plain film of the abdomen was not taken in the Emergency Ward. I should have felt the need for more help, as I do now.

I believe I have a fair idea of what the pathologic physiology may have been, but I do not know what the diagnosis was. I suspect that there was an inflammatory process, probably an abscess opposed against the lower large bowel, causing this train of symptoms. The etiology of the inflammatory process is in question. Among the salient points in the history is the striking duration of the pain for a year, with episodes of increased severity in which it tended to be emphasized in the left lower quadrant and was associated with diarrhea, and later with vomiting. The stools contained no mucus and no blood, and this finding was confirmed by the proctoscopic examination, which showed no break in the mucosa. Another important feature is the fact that the catamenial history was abnormal. A menstrual period had been missed six months before admission; thereafter, her periods were scanty and for either two or three months did not occur. Finally, the physical examination indicates that there was an inflammatory process in the left lower quadrant, within which there was a mass 6 cm. in diameter. That this mass could be felt abdominally as well as on pelvic examination I think is significant because small masses—6 cm. is not very large—originating in the pelvic organs are rarely felt on abdominal examination.

I should like to narrow the discussion down to processes in the genital and gastrointestinal tracts. The symptoms related to one tract were probably the direct result of primary disease in the other. I suspect that the genital tract was not the primary site of disease. Ectopic pregnancy was certainly considered by her physicians, but the story was much too long and other factors were against it. Endometriosis might be mentioned only to be ruled out. This would entail endometriosis not only of the genital organs but also of the bowel, presumably the sigmoid. I consider this unlikely because of the intermittent nature of her discomfort and the inflammatory reaction found. Tumors of the left ovary, including cysts or solid tumors, which might have become twisted, seem unlikely. Pelvic inflammatory disease bothers me most of all. This woman had an unhappy marital life, I gather, and she was of rather low intelligence—both of which often go with pelvic inflammatory disease. The catamenial history, however, is not that of pelvic inflammatory disease, in which there is usually much greater irregularity in flow, both in amount and in timing. The type of pain was not that related to the pelvic organs so I suspect that the primary disease was in the gastrointestinal tract and that these menstrual changes were secondary to an inflammatory process arising in the intestinal tract.

The duration of the symptoms suggests that this was not an acute process; it was not a gastroenteritis. There may possibly have been a congenital malformation such as a Meckel diverticulum or band that was

*Assistant surgeon, Massachusetts General Hospital.

not making itself known. Meckel's diverticulum does behave this way and does make itself evident at such an age. I think it is rarely associated with a mass other than that due to small-bowel obstruction, and at the age of twenty-seven it usually presents as small-bowel obstruction. Regional ileitis is more commonly palpated in the right lower quadrant and rarely produces masses in the left quadrant, although the history is certainly consistent with an ileitis. Ulcerative colitis seems farfetched: the patient had episodes that were acute, with diarrhea, and periods when she was relatively well. Diverticulitis of the colon, the sigmoid particularly, with perforation of one of these diverticula and abscess formation, is a definite possibility. In a large group of such cases in which operation was performed, Dr. Reginald H. Smithwick[1] found only 1 patient in the third decade of life. And in a later group[2] only 1 patient was operated on at such an early age. In other words symptoms severe enough to warrant surgical attention rarely occur in this younger age group. Patients with diverticulitis certainly do have this type of discomfort, often described as an ache, with acute episodes of pain. On the basis of age alone, however, I should rule out diverticulitis.

The other likely site of disease is the appendix. There are many objections to appendicitis with abscess formation as a cause of this picture. It is unusual for appendicitis to give symptoms of a year's duration, and there were four distinct attacks of pain. The attack that took place before admission was quite severe and required hospitalization and probably the use of antibiotics. That in itself tends to mask the subsequent life history of an acutely inflamed appendix, so that on the basis of duration of the symptoms alone I do not want to rule out appendicitis. The position of the mass means very little because the appendix can wander over into the left lower quadrant, lie up against the bowel and cause diarrhea.

The other rare and unusual possibilities I am not even going to mention.

I should believe that this was an inflammatory process that was plastered against the lower colon. Whether it arose from the left tube and ovary or from the appendix I do not know, but I prefer to say that the appendix was responsible.

Clinical Diagnosis

Tubo-ovarian abscess.

Dr. Gordon A. Donaldson's Diagnosis

Inflammatory disease of appendix.

Anatomical Diagnosis

Acute salpingitis, with salpingo-ovarian abscess.

Pathological Discussion

Dr. Winfield S. Morgan: Dr. Hopkins, would you give the impression on the ward and describe the surgical findings?

Dr. Robert W. Hopkins: We were equally confused about the diagnostic possibilities and listed practically all that Dr. Donaldson has mentioned. We were aided by the presence of a tattoo on the left thigh, however, and made the preoperative diagnosis of tubo-ovarian abscess.

This patient did have an extensive inflammatory process involving the left tube and ovary. The abscess cavity itself was perhaps 5 to 8 cm. in diameter, but the inflammatory mass that surrounded it was considerably larger and involved the sigmoid and surrounding peritoneum. We removed the mass, and the patient made an uneventful recovery.

Dr. Morgan: The specimen that we received in the laboratory consisted of the ovary and tube. On section there was cystic dilatation of a portion of the tube that contained greenish, purulent material, and on microscopical examination this had the typical features of acute and chronic salpingitis, with abscess formation.

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1. Smithwick, R. H. Experiences in surgical management of diverticulitis of sigmoid. *Am. J. Surg.* **115**:969-985, 1942.
2. Welch, C. E., Allen, A. W., and Donaldson, G. A. Appraisal of resection of colon for diverticulitis of sigmoid. *Ann. Surg.* **138**:332-343, 1953.

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PIONEER AND PATRON

THERE appears in the column *Nova et Vetera,* in the *British Medical Journal* of February 13, 1954, a brief summary of the life and contributions to medicine of Richard Mead, "Pioneer and Patron." Although not mentioned in this account, Mead, who was John Radcliffe's professional legatee, was the second owner of the Gold-Headed Cane, which also came to him from Radcliffe.

Radcliffe, who had come into possession of the cane in 1689, the year of Sydenham's death, was a bachelor and the most popular practitioner in London in his day. Skillful, handsome and witty, he was also not infrequently rude and abusive. His prescription for success, given to Mead, to "use all mankind ill," has unfailingly been coupled with his name. Physician to William and Mary and to Queen Anne, Radcliffe left an estate of nearly £100,000, much of it to St. Bartholomew's Hospital and to Oxford University, where it bore fruit in the Radcliffe Infirmary, the Radcliffe Observatory and the Radcliffe Library.

Mead, born in 1673, the son of a Nonconformist minister, was educated at Utrecht, Leyden and Padua; he took his doctor's degree in philosophy and physic at the Italian university in 1695. Rising rapidly in his profession he was elected to the Royal Society in 1703 and became a physician to St. Thomas's Hospital in the same year. The rewards of merit, not retarded by Mead's pleasant personality, came in logical order—a readership in anatomy to the Company of Barber Surgeons, the vice-presidency of the Royal Society and a doctor's degree in medicine from Oxford, which made him eligible for his fellowship in the Royal College of Physicians. In this body he became in time Harveian Orator and eventually had the distinction of refusing the presidency.

At the age of forty-one Mead succeeded to Radcliffe's house and practice in Bloomsbury Square—he had already been presented with the Gold-Headed Cane—and continued, unmindful of Radcliffe's injunction, to treat all mankind well. When Watteau, as the story is told in *Nova et Vetera,* came to Mead for treatment of his tuberculosis, Mead gave him two commissions as ancillary therapy, and when his friend Dr. Freind was confined to the Tower for political reasons Mead took care of his practice, refused to prescribe for the prime minister, Sir Robert Walpole, until Freind had been released and, as a final act of generosity, presented Freind with the entire sum received from his patients during the incarceration!

In addition to his private practice, said to have been worth from £6000 to £7000 a year, Mead was a pioneer in public health, a patron of the arts and a collector of books. The last twenty-four years of his life were spent in Great Ormond Street, "more in the sunshine of life than any other man," in the words of Dr. Johnson. Unfortunately, on his death in 1754 his art collection and his library of over 10,000 volumes were broken up and sold at auction. No museum or library, therefore, bears his name, and his greatest monument is not identified with him. "For it was he," according to *Nova et Vetera,* "who persuaded the bookseller Thomas Guy to erect a new hospital at a cost of £18,793, increased by an endowment of £200,000 on Guy's death in 1724."

PROGNOSIS AFTER HEART ATTACKS

THE most important factor in the prognosis of heart disease appears to be the survival of the initial attack. Such a deduction, which is not so obvious as it seems, results from a study of survivorship among a group of white male standard risks of the Metropolitan Life Insurance Company who became disabled by heart disease, later recovering sufficiently to return to work. An important figure undivulged is the mortality rate from the initial attack.

Regardless of the type of disease that caused the attack, more than 70 per cent of the victims were alive after five years; in the cases in which arterioscle-

rosis was the sole detectable lesion 85 per cent of the patients survived the five-year period and 70 per cent lived for ten years or more. Where coronary occlusion was an added factor the prognosis was less favorable, but even with this ubiquitous complication the ten-year survival rate was over 50 per cent.

Many persons who have been disabled by heart disease, moreover, recover to the point of resuming various types and degrees of activity, thereby benefiting both physically and emotionally; fear of the risk that might be incurred by a return to work is one of the chief obstacles to a tempered rehabilitation.

FELLOWS OF THE ROYAL SOCIETY

THE election last March of Professor A. Bradford Hill to fellowship in the Royal Society not only gratifies his many friends in America but must appeal to those who have made up his audiences in this country as an example of the ultimate triumph of the statistical method made attractive. One of a list of twenty-five distinguished persons selected for this honor, Professor Hill occupies the chair of medical statistics and is director of the Department of Medical Statistics and Epidemiology at the London School of Hygiene and Tropical Medicine; he is honorary director of the Statistical Research Unit of the Medical Research Council.

Professor Hill has been a contributor to the *Journal* on two occasions. "The Clinical Trial," a lecture delivered before the Department of Preventive Medicine of the Harvard Medical School on May 28, 1952, was published in the issue of July 24 of that year and "Observation and Experiment," delivered as the Cutter Lecture on Preventive Medicine at the Harvard School of Public Health on March 25, 1953, was published in the issue of June 11, 1953.

In recent years he has been active in the evaluation of new therapies, in conjunction with his colleagues of the Medical Research Council. In view of the great increase in the number of useful drugs and the extravagant claims that have been made for so many of them, the importance of this work is beyond question. In collaboration with Dr. R. Doll, Professor Hill has also made valuable contributions to the study of the relation between smoking and cancer of the lung.

Also of interest to the medical profession is the election to the Society of another English scientist who, like Professor Hill not a physician, is, like him, working in close collaboration with physicians. Dr. Rosalind Pitt-Rivers, a bachelor of science, a master of science and a doctor of philosophy from the University of London, is currently engaged in research at the Massachusetts General Hospital on the products of the thyroid gland.

Not to be confused with the relatively youthful Royal Society of Medicine, founded a scant half century ago, the "Invisible College" came into existence in 1645 under the impetus of such original thinkers as Robert Boyle, Robert Hooke, Richard Lower and John Mayow, the four Oxonians who carried on their studies of the circulation where Harvey had left off. The organization was chartered by Charles II in 1662 as the Royal Society of London, and two years later began the publication of its famous *Transactions*, which has continued to the present day.

BULLARD PROFESSOR RETIRES

ON the occasion of his retirement from active teaching and hospital service it is fitting to make note of the impact that Stanley Cobb has made felt on his special branch of medicine. As Bullard Professor of Neuropathology at the Harvard Medical School since 1926 and chief of the Psychiatry Service at the Massachusetts General Hospital since 1934 he has been one of those responsible for bringing mind and matter together in modern medicine — for introducing psychiatry to science and for making the psychosomatic concept something to be viewed with the dispassionate eye of the trained investigator.

The training of Dr. Cobb's own superior talents made him particularly fitted for this work. A graduate of Harvard Medical School in 1914, he served as surgical house officer at the Peter Bent Brigham Hospital, then engaged in research in physiology and psychiatry at Johns Hopkins Medical School. After his army service during World War I he became an instructor at the Harvard Medical School and assistant neurologist at the Massachusetts General Hospital until his appointment as assistant professor of neuropathology in 1920, and associate professor in 1923. In 1924 and 1925 he studied at Oxford, Paris and Berlin as a Rockefeller fellow, becoming visiting physician for neurology at the Boston City Hospital on his return, a post that he held until his present appointment at the Massachusetts General Hospital.

His career and its fruits are suggested by the citation with which he received an honorary degree from the University of Maryland in 1952:

> One of the eminent neurologists and psychiatrists in this country . . . , he was among the first to recognize the importance of psychoanalysis in psychiatry and medicine . . . and he is recognized in contemporary psychiatry as a scholar, investigator and teacher. . . . His influence in the field has been great and many of his students occupy leading positions in American neurology and psychiatry today.

It is anticipated that Stanley Cobb's release from academic duties will free him for still greater contributions to medicine in general.

In September last, a girl at Vienna, who labored under an aberration of intellect, attempted to destroy her life by swallowing a quantity of pins. . . . There were no less than 242 pins passed, all of them of a black color. The girl is now in a fair way of recovery. — London Lancet

Boston M. & S. J., *June 21, 1854*

MASSACHUSETTS MEDICAL SOCIETY

ANNUAL GOLF TOURNAMENT

The results of the annual golf tournament held at the Wollaston Golf Club on May 19, 1954, are as follows: low net and name on Burrage Bowl, Dr. Francis H. Carr, Worcester; second low net, Dr. John J. Todd, Milton; low gross, Dr. John F. Curran, Jr., Worcester; and second low gross, Dr. Roy J. Heffernan, Jamaica Plain.

DEATHS

McNAMARA — John McNamara, M.D., of Taunton, died on May 17. He was in his sixty-first year.

Dr. McNamara received his degree from Tufts College Medical School in 1918. He was director of the Board of Health, Taunton.

He is survived by his widow, three daughters and a son.

NELLIGAN—John P. Nelligan, M.D., of Cambridge, died on May 29. He was in his seventy-seventh year.

Dr. Nelligan received his degree from Harvard Medical School in 1902. He was a member of the staff of the Mount Auburn Hospital and formerly president of the Cambridge Medical Improvement Society and a councilor of the Massachusetts Medical Society.

He is survived by his widow, two daughters, two sons, a brother and nine grandchildren.

NUTT—Walter E. Nutt, M.D., of Methuen, died on April 18. He was in his eightieth year.

Dr. Nutt received his degree from Baltimore University School of Medicine in 1899. He was a fellow of the American Medical Association and was formerly physician, Henry C. Nevins Home for Aged People, Methuen.

He is survived by a sister and several nieces and nephews.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

Orthopedic Clinic	Date	Clinic Consultant
Gardner	July 6	Carter R. Rowe, M.D.
Haverhill	July 7	William T. Green, M.D.
Brockton	July 8	George W. Van Gorder, M.D.
Salem	July 12	Paul W. Hugenberger, M.D.
Lynn*	July 12	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Springfield	July 13	James D. Fisher, M.D.
Worcester	July 16	John W. O'Meara, M.D.
Pittsfield	July 21	Edward J. Coughlin, Jr., M.D.
Hyannis	July 22	Paul L. Norton, M.D.
Greenfield	Aug. 5	Charles L. Sturdevant, M.D.
Lowell	Aug. 13	Albert H. Brewster, M.D.
Fall River	Aug. 23	David S. Grice, M.D.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Clinic.

Rheumatic-Fever Clinic	Dates
North Reading	July 6, 13, 20, 27
Fitchburg	July 7, 14, 21, 28

Plastic Clinic	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

NONCLINICAL NOTES

HONORARY DEGREE

Dr. James W. Manary, superintendent and medical director of the Boston City Hospital since 1935, received an honorary degree of Doctor of Science from Boston College on June 9.

NOTICES

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

The meetings of the New England Society of Anesthesiologists for the coming year will be held as follows:

October 1, 1954, at Hanover, New Hampshire
December 3, 1954, at Boston, Massachusetts
February 4, 1955, at New Haven, Connecticut
April 1, 1955, at Boston, Massachusetts

SOCIETY MEETINGS AND CONFERENCES

JUNE 17–21. Pan American Congress of Ophthalmology. Page 540, issue of March 25.

JUNE 19 and 20. Society for Investigative Dermatology. Page 540, issue of March 25.

JUNE 22. South End Medical Club. Page 1014, issue of June 10.

JUNE 23. Tufts Medical Alumni AMA Dinner. Page 585, issue of April 1.

JULY 6–AUGUST 23. Consultation Clinics for Crippled Children in Massachusetts. Notice above.

JULY 22 and 23. International College of Surgeons. Regional Meeting. Page 828, issue of November 12.

JULY 23–29. International Cancer Congress. Page 914, issue of November 26.

JULY 26–31. International Congress of Gynecology and Obstetrics. Page 400, issue of March 4.

AUGUST 1–7. Pan-American Congress of Pediatrics. Page 850, issue of May 13.

AUGUST 17–20. Argentine Congress of Thoracic Surgery. Page 708, issue of April 22.

SEPTEMBER 6–10. International Poliomyelitis Congress. Page 399, issue of March 4.

SEPTEMBER 7–10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.

SEPTEMBER 12–15. Second International Congress of Cardiology, Washington, D.C.

SEPTEMBER 13–15. American Association of Blood Banks. Page 968, issue of June 3.

SEPTEMBER 16–18. American Heart Association. Annual Scientific Sessions, Washington, D.C.

OCTOBER 1 AND DECEMBER 3, 1954. FEBRUARY 4 AND APRIL 1, 1955. New England Society of Anesthesiologists. Notice above.

SEPTEMBER 22. New England Pediatric Society. Page 968, issue of June 3.

OCTOBER 8 and 9. Academy of Psychosomatic Medicine. Page 748, issue of April 29.

OCTOBER 27. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, JUNE 24

THURSDAY, JUNE 24

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*9:00–10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*11:00 a.m. Thoracic Conference. The Treatment of Mitral Stenosis in the Aged. Dr. William Bernhardt. Main Amphitheater, Peter Bent Brigham Hospital.

(Notices concluded on page xxvii)